

Nos. 23-2402, 23-2403, 23-2411

**United States Court of Appeals
for the Federal Circuit**

SYDNEXIS INC.,

Appellant,

v.

EYENOVIA, INC.,

Appellee.

*Appeal from the United States Patent and Trademark Office, Patent Trial and
Appeal Board in Nos. IPR2022-00384, IPR2022-00414, IPR2022-00415*

APPELLANT'S OPENING BRIEF

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Dated: February 1, 2024

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REPRESENTATIVE CLAIMS

U.S. Patent No. 10,842,787

1. A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising [a] from 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, [b] wherein the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, [c] wherein the stabilized ophthalmic composition is a liquid, and [d] wherein the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks [d.1] under a storage temperature of from about 20° C. to about 70° C. and [d.2] relative humidity from about 50% to about 80%.

Appx000227 at Claim 1.

U.S. Patent No. 10,940,145

1. A kit comprising:

a. a vial comprising a pharmaceutical composition, the pharmaceutical composition comprising:

- i. about 0.01 mg/g to about 0.5 mg/g of atropine or atropine sulfate;
- ii. water; and
- iii. a buffer; and

b. instructions for use.

Appx000293 at Claim 1.

U.S. Patent No. 10,888,557

1. A method of treating progression of myopia or reducing the progression rate of myopia in an individual in need thereof, comprising administering to an eye of the individual

(a) an aqueous solution comprising atropine or atropine sulfate and less than about 10% of a degradant of atropine or atropine sulfate formed from degradation of the atropine or atropine sulfate and

(b) a buffering agent.

Appx000359 at Claim 1.

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**UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT**

CERTIFICATE OF INTEREST

Case Number 2023-2402, 2023-2403, 2023-2411

Short Case Caption Sydnexis, Inc. v. Eyenovia, Inc.

Filing Party/Entity Sydnexis, Inc.

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Name: Michael T. Rosato

FORM 9. Certificate of Interest

Form 9 (p. 2)
March 2023

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	2. Real Party in Interest. Fed. Cir. R. 47.4(a)(2).	3. Parent Corporations and Stockholders. Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. <input checked="" type="checkbox"/> None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. <input checked="" type="checkbox"/> None/Not Applicable
Sydnexis, Inc.		

☐ Additional pages attached

FORM 9. Certificate of Interest

Form 9 (p. 3)
March 2023

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable

☐ Additional pages attached

Michael J. Hostetler		

5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ Yes (file separate notice; see below) ☒ No ☐ N/A (amicus/movant)

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☒ None/Not Applicable

☐ Additional pages attached

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STATEMENT OF RELATED CASES

Under Federal Circuit Rule 47.5(a), counsel for Appellant Sydnexis, Inc. states that no appeal from the same proceeding was previously before this or any other appellate court nor will this Court's decision directly affect or be affected by any pending cases.

JURISDICTIONAL STATEMENT

Sydnexis appeals from the final judgments of the U.S. Patent Trial and Appeal Board entered on July 13, 2023. Appx000054-000055, Appx000105-000107, Appx000159-000161. Sydnexis timely filed notices of appeal on September 14, 2023. Appx001148-001152, Appx010558-01562, Appx011182-011186. This Court has jurisdiction under 28 U.S.C. §1295(a)(4)(A).

INTRODUCTION

The Board’s final written decisions should be set aside for holding the claims obvious without finding the asserted prior art disclosed every element of the claims. The decisions also impermissibly shifted the burden of proof from the petitioner (Eyenovia) to the patent owner (Sydnexis).

The challenged patents are directed to an aqueous ophthalmic solution of low-concentration atropine that is buffered. In U.S. Patent No. 10,842,787 (the ’787 patent), for example, the claims specifically recite using “a buffering agent to provide a pH of from about 4.8 to about 6.4.” Appx000227. The meaning of buffering as used in the claims was undisputed: it must maintain or control the pH. But the prior art reference (Akorn¹) the Petition relied upon for disclosure of this limitation did not disclose that its solution was buffered. Nor did it disclose the

¹ Akorn Atropine Care™ (atropine sulfate ophthalmic solution), NDA 206289 Product Label (Revised July 2014) (Appx001280-001284).

amounts of the ingredients (phosphate salts) alleged in the Petition to satisfy the buffering limitations. The Board never found that it did. Instead, the Board inverted the burden of proof, and required Sydnexis to prove it would be impossible for these phosphates to buffer at the implicated pH under any circumstances.² The Board's conclusion of obviousness was thus erroneously predicated on a finding of what *could have been done*, rather than what actually was disclosed, and on an impermissible shifting of the burden of proof.

Because it erroneously *focused on possibilities*, the Board committed a second legal error. It brushed aside the inventors' discovery of an unknown stability problem in low-concentration atropine solutions. But because the stability problem was not known in the prior art, Petition's asserted motivation to modify was unsupported. Having erroneously placed the burden of proof on the patent owner, and because they fail to satisfy the legal standards for obviousness, the Board's decisions should be vacated.

The Board's errors about the applicable legal standards discussed above bled into its factual findings, which are not supported by substantial evidence. First, it—without explanation—disregarded evidence (1) that Chia's ophthalmic solution already was stable without buffering and (2) that pH adjustment without buffering

² As discussed separately, the record shows the phosphates were not necessarily buffering.

was the indicated means for balancing stability with patient comfort. Second, it erroneously concluded that phosphate salts employed in a solution pH outside their pharmaceutical buffering range would satisfy the buffering requirements of the claims by serving as a nonfunctional or ineffective buffer. The Board's conclusions of obviousness should therefore be set aside because its underlying fact-findings lack substantial evidence.

STATEMENT OF THE ISSUES

1. Did the Board legally err by:
 - a. shifting the burden of proof to the patent owner and holding the challenged claims obvious based on possibilities rather than prior art disclosure by the asserted references; and
 - b. disregarding Sydnexis's discovery of an unknown problem and finding motivation based on what *could* have been done rather than what *would* have been done?
2. Does substantial evidence support the Board's motivation to add buffering to Chia's already-stabilized low-concentration atropine solution or the Board's departure from the pharmaceutical buffering range of phosphates salts?

STATEMENT OF THE CASE

I. The Challenged Patents

The challenged patents describe a stabilized, aqueous, low-concentration atropine solution that is buffered to provide a pH of from about 4.8 to about 6.4 and can be used for treating pre-myopia, myopia, and progression of myopia. *E.g.*, Appx000227 (97:32-44).³ Myopia is an axial elongation of the eye that begins in grade school and generally progresses until the growth of the eye is complete. Appx000183 (10:44-47). Previously, higher-concentration atropine solutions had been used to treat myopia, but those higher concentrations caused significant side effects, such as glare from pupillary dilation and blurred vision. Appx000184 (12:21-24).

But after many experiments, the inventors “recognize[d] that ... atropine[] liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present[ed] stability challenges that [we]re less so in higher concentrations (e.g. 0.1-1%).” Appx000183 (10:15-19); *see also* Appx009672-009674. Specifically, when evaluating the impact of atropine concentration on atropine stability, the inventors discovered that atropine degraded in aqueous solution at a faster rate when the atropine concentration was very low than when the atropine concentration was

³ The specifications of the other two challenged patents contain equivalent disclosures. Appx009836-009837.

higher. Appx000217-000218 (Tables 14A, 15, 16), Appx009673-009674. That accelerated degradation made the solution more acidic. Appx000219 (Table 18). After identifying the stability problems for low-concentration atropine solutions, the inventors discovered that using a buffering agent to provide a pH within the critical zone of 4.8 to 6.4 mitigated the instability issue that they had discovered. Appx000220-000222 (Tables 23A, 24A, 25A, 26A, 27A, 30), Appx009674.

As explained during prosecution, the prior art did not recognize the stability problem of dilute atropine, and a POSA would not have had a reason to incur the additional time and expense to formulate a buffered low-concentration atropine solution without knowing about that stability problem. Appx003502-003503. Applicants explained that maintaining the pH specified in the pending claims was critical to providing better stability for low-concentration atropine solutions, that degradation increased when tested at higher than the claimed value of 6.4, and that pH did not stably remain above 4.0 when tested at lower than the claimed 4.8 value. Appx003504-003505. Because the '787 patent recites a “stabilized” liquid ophthalmic composition that requires “a buffering agent to provide a pH of from about 4.8 to about 6.4,” which none of the prosecution references disclosed, and because the prior art failed to recognize the stability problem of low-concentration atropine solutions after storage for an extended time, the Examiner allowed the

claims. Appx003504-003505, Appx003554, Appx003559-003561, Appx003669, Appx003792.

The specification explains that a buffering agent or buffer “provide[s]” pH “control or maintenance.” Appx000196 (36:41-46), Appx009667-009670; *see also* Appx010736 (stating that the claims should be construed “in accordance with the ordinary and customary meaning as understood by a POSA and the prosecution history”), Appx011041 (“Petitioner agrees that the ordinary meaning of terms should apply in this proceeding.”). Reading the claims in light of the specification’s ordinary meaning precludes reading “buffer” to mean something that is nonfunctional or inoperative for controlling and maintaining the pH (i.e., fails to address the disclosed problem). The patent specifically discloses that mere inclusion of disodium hydrogen phosphate, sodium dihydrogen phosphate, or a combination thereof, does not necessarily satisfy the buffering limitations, because these same excipients can be made into a tonicity adjusting agent or a buffering agent. Appx009669; *see* Appx000180 (3:52-62), Appx000182 (7:60-8:3), Appx000200-000201 (44:54-65, 45:1-9), Appx000226 (96:43-53) (all discussing tonicity); *see* Appx000180 (3:45-51), Appx000182 (7:53-59), Appx000188-000189 (20:65-21:5, 21:29-42, 22:14-34), Appx000226 (96:37-42) (all discussing buffering). Whether the excipients constitute a buffering agent depends at least on the amounts of the

excipients used and the pH of the solution in which they are used. Appx009669-009670.

II. Relevant Ground References

A. Chia

Chia is a journal article that describes administering low-concentration atropine eyedrops to children every day for two years to treat myopia. Appx001272. Chia discloses the “[t]rial medication consisted of the appropriate dose of atropine sulfate with 0.02% of 50% benzalkonium chloride as a preservative.” Appx001273. Accordingly, Chia does not disclose buffering or a pH of 4.8 to 6.4.

B. Akorn

Akorn describes a 1% atropine sulfate eyedrop solution approved for uses other than myopia treatment. Appx001280. Akorn lists the following ingredients:

Each mL of Atropine Sulfate Ophthalmic Solution USP, 1% contains:
Active: atropine sulfate 10 mg equivalent to 8.3 mg of atropine.
Inactives: benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.

Appx001282. Other than atropine and benzalkonium chloride, Akorn does not disclose the amounts of the ingredients. It also does not disclose the specific solution pH obtained within the limits of 3.5 to 6.0 using the hydrochloric acid and/or sodium hydroxide. It was undisputed below that hydrochloric acid, sodium hydroxide, and benzalkonium chloride are not buffering agents. Appx009656, Appx009835.

C. Kondritzer

Kondritzer is a journal article that studies the hydrolysis of atropine. Kondritzer determined the pH of minimum hydrolysis at various temperatures and calculates the hydrolytic rates at these pH values. Appx001286. Kondritzer also calculates the half-life of atropine in aqueous solutions having various pH values and temperatures. Appx001286. Kondritzer concludes that “[t]he pH for maximum stability of atropine in sterile aqueous solution varies between 4.11 at 0° and 3.24 at 100°.” Appx001289.

Kondritzer reports that the half-life of atropine at room temperature is 1800 years, 811 years, 266 years, and 27 years at pH 4.0, 4.5, 5.0, and 6.0, respectively. Appx001288 (Table III). It was undisputed below that atropine was thus expected to have a stable shelf-life of years at each of these pH values. Appx009718-009720.

III. IPR Proceedings

The only petition grounds addressed by the Board’s final written decisions asserted the claims were unpatentable as obvious over Chia, Akorn, and Kondritzer. Appx000053, Appx000159, Appx000105, Appx010736-010737, Appx010109-010110, Appx000576-000577 (asserting obviousness over Chia and Akorn). Because Chia’s efficacious low-concentration atropine solution was unbuffered, Petitioner argued that Akorn disclosed the buffering limitations. Appx010737, Appx010740-010741. The only support that Petitioner could articulate was that

Akorn listed as inactive ingredients “dibasic sodium phosphate [and] monobasic sodium phosphate.” Appx010740. Sydnexis responded that Akorn did not state that it included a buffer at all, that Akorn attributed solution pH to excipients known not to be buffering agents (hydrochloric acid and sodium hydroxide), that Akorn did not reveal its actual solution pH or the concentrations of the phosphates, and that Petitioner had thus failed to prove that Akorn disclosed the buffering limitations. Appx010982-010983, Appx010990-010993. Moreover, based on the pharmaceutical buffering range for phosphates (6.2-8.2) disclosed in Petitioner’s pharmaceutical buffer reference (Waterman), Sydnexis noted that there was no overlap with the USP pH limits of 3.5 to 6.0 required in the Akorn reference. Appx010991, Appx010995-010997.

Petitioner then submitted several reply references discussing biological or cell “buffers,” not ophthalmic or pharmaceutical buffers. Appx008943-009077. According to Petitioner, those references purportedly showed that phosphates could sometimes, under some circumstances, have a pK_a of under 7.2 and may be able to buffer as low as 5.4. Appx011043-011044. Relying on those reply references, the Board found that it was *possible* that phosphates could buffer within the USP⁴ limits of 3.5 to 6.0. Appx000041-000044. The Board also found that a nonground reference

⁴ “USP” stands for National Formulary of the U.S. Pharmacopeia, which imposes quality standards for medicines, such as pH limits. *See* Appx000040, Appx010961.

discussing ophthalmic solutions recommended the use of buffers to maintain pH at the appropriate level as needed while minimizing buffer capacity to provide patient comfort and compliance. Appx000045-000046. Finally, the Board found that Akorn “disclose[d] a pH range of 3.5 to 6.0.” Appx000046. Based solely on those findings, (i.e. (1) the possibility of buffering under circumstances not disclosed here and (2) the general recommendation of a nonground reference to use a buffer when “appropriate”), the Board concluded the claims were obvious. In so concluding, the Board disregarded the inventors’ discovery of an unknown problem, stating that “regardless of whether the problem of the stability of atropine at low doses was unexpected,” the use of a buffer to maintain pH was exactly how a buffer was supposed to be used. Appx000047.

SUMMARY OF THE ARGUMENT

The petition grounds accepted by the Board rely on one asserted reference—Akorn—disclosing buffering its atropine ophthalmic solution to maintain a solution pH between 4.8 and 6.0. The Board legally erred in at least two ways when it held the claims obvious. First, Akorn does not disclose buffering its ophthalmic atropine solution, and the Board never found that it did. Instead, the Board found that it was *possible* under certain conditions (not inherently present in Akorn) that the phosphate salts listed in Akorn *could* buffer within the implicated pH limits. But mere possibilities do not establish obviousness. Moreover, the Board impermissibly

shifted the burden to Sydnexis by requiring it to prove that it was impossible for the phosphate salts to buffer at the indicated pH rather than requiring the Petitioner to prove its case that Akorn disclosed buffering the ophthalmic atropine solution at the indicated pH.

Second, the Board's blinkered focus on possibilities caused it improperly to brush aside the inventors' discovery of an unknown instability problem in low-concentration atropine aqueous solution. The Board focused on what a POSA *could* have done, if they had known of the problem, rather than what a POSA *would* have done given they did not know about the problem. The Board's conclusion of motivation to modify to address an unknown problem was a legal error and reflects impermissible hindsight bias that has no place in an obviousness analysis. Accordingly, the Board's decisions should be reversed.

The Board's errors about the applicable legal standards discussed above bled into its factual findings, which are not supported by substantial evidence. First, it inexplicably disregarded the evidence that Chia's ophthalmic solution as used therapeutically already was stable without buffering and that pH adjustment without buffering was the indicated means for balancing stability with patient comfort. Second, it erroneously concluded that phosphate salts employed in a solution pH outside their pharmaceutical buffering range would satisfy the buffering requirements of the claims by serving as an ineffective or inoperative buffer. The

Board’s conclusions of obviousness should therefore be reversed because its underlying fact-findings lack substantial evidence and the record below provides no alternative basis for a remand.

ARGUMENT

I. Standard of review

“Obviousness presents an ultimate legal question with numerous underlying factual findings.” *Cyntec Co., Ltd. v. Chilisin Elecs. Corp.*, 84 F.4th 979, 984 (Fed. Cir. 2023) (citations omitted). This Court “review[s] the conclusion of obviousness *de novo*.” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 972-73 (Fed. Cir. 2014). Underlying factual findings are reviewed for substantial evidence. *Intel Corp. v. PACT XPP Schweiz AG*, 61 F.4th 1373, 1378 (Fed. Cir. 2023).

“In an inter partes review ..., the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (quoting 35 U.S.C. §316(e)). “[T]hat burden never shifts to the patentee.” *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). And it includes “the burden of producing evidence to support a conclusion of unpatentability under §102 or §103.” *In re Magnum*, 829 F.3d at 1376 (citing *Dynamic Drinkware*, 800 F.3d at 1379). Thus, for an obviousness analysis, “the notion of burden-shifting is inapposite

because the patentee’s position is that the patent challenger failed to meet *its* burden of proving obviousness.” *Id.*

II. The Board committed prejudicial legal error by requiring the patent owner to prove it was impossible for Akorn’s phosphates to satisfy the claimed buffer limitation.

When a petitioner attempts to prove obviousness based on a combination of references in the prior art, the petitioner must first show that the elements of the claim are disclosed in the asserted prior art. *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (citing *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006)). Here, the Board found only that it *might be possible* for the phosphates listed in Akorn to buffer under conditions not disclosed in Akorn. The Board thus shifted the burden of proof erroneously to Sydnexis to prove that it was *impossible* to use the phosphate salts to buffer at the indicated pH. Accordingly, the Board’s decision should be set aside.

A. The Board erroneously held the claims obvious based on the mere possibility that the phosphate salts in Akorn could be used to buffer.

To prevail on obviousness, Petitioner had the “burden to prove that all claimed limitations [we]re disclosed in the prior art.” *Par Pharm.*, 773 F.3d at 1194. The Board thus cannot hold claims invalid as obvious unless it finds the specific prior art references asserted in the relevant ground disclose all of the claim limitations. *Id.*; *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that if “[t]he prior art ... does not disclose or suggest” a claim limitation, then “the PTO has not established

the prima facie obviousness of the claimed subject matter”). Here, the Board did not find that the ground references (Chia, Akorn, and Kondritzer) disclosed all the limitations of Sydnexis’s claims. It therefore erred in holding the claims obvious.

The dispute on appeal centers on the buffering limitation. In the ’787 patent, this limitation states: “wherein the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4.” Appx000227 (97:32-44), Appx000038-000039. It was undisputed below that “buffering” has its plain meaning, which requires that the agent control or maintain the indicated pH. Appx000013-000014, Appx010736, Appx010985-010986, Appx010989, Appx011041. Petitioner relied exclusively on Akorn to disclose the buffering limitation, arguing that Akorn expressly disclosed using a buffer system to maintain a solution pH of 3.5 to 6.0. Appx010737, Appx010740, Appx010744-010745. As explained in detail below, Akorn did not disclose that its ophthalmic atropine solution employed a buffering agent to provide a pH of 4.8-6.0, and the Board did not find that it did.

It was undisputed below that Akorn never mentions buffering. *See* Appx010991 (citing Appx009690-009692, Appx009696-009697). Petitioner’s argument that Akorn disclosed using a buffering agent to maintain a solution pH of 4.8 to 6.0 thus rested solely on the list of inactive ingredients in Akorn. That list provided:

- “benzalkonium chloride 0.1 mg (0.01%)”;
- “dibasic sodium phosphate”;
- “edetate disodium”;
- “hypromellose (2910)”;
- “monobasic sodium phosphate”;
- “hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0)”;
- “water for injection USP.”

Appx001282, Appx009826-009829. Importantly, Petitioner’s expert testified that, of those inactive ingredients, only the phosphate salts could be buffering agents. Appx009835.

Petitioner’s argument assumed that mere disclosure of phosphate salts as inactive ingredients established that they were present as a buffering agent to provide a pH between 3.5 and 6.0. But Akorn does not attribute any pH effect to the phosphate salts. Appx001282. Instead, it exclusively attributes the solution pH to excipients (hydrochloric acid and sodium hydroxide) that Petitioner’s expert agreed *were not buffering agents*. Appx009835; *see also* Appx009824-009825 (distinguishing between Akorn’s disclosure of “dibasic sodium phosphate [and] monobasic sodium phosphate” and “then a pH adjuster, hydrochloric acid and sodium hydroxide”), Appx001282 (explaining that “hydrochloric acid and/or

sodium hydroxide may be added to *adjust* pH”),⁵ Appx010992-010993. And other than “benzalkonium chloride 0.1 mg (0.01%),” Akorn does not reveal the concentrations of those inactive ingredients. Appx001282, Appx009827-009829. Nor does Akorn disclose the actual solution pH of its formulation. Appx009833, Appx009693. Petitioner’s argument thus assumed that any mention of phosphate salts in the list of inactive ingredients established they are present as a buffer (i.e., maintaining the pH) between pH 4.8 and 6.0.

The Board held the claims unpatentable without making any finding that Akorn disclosed its ophthalmic solution comprised sufficient phosphates to constitute a buffering agent to provide a pH of 4.8-6.0. At the outset, the Board noted Sydnexis’s contentions that “Akorn does not state that it employs a buffering agent to control or maintain pH of its atropine solution,” “that the phosphate salts disclosed in Akorn are not identified as buffering agents,” and “that there is no indication in Akorn that the listed phosphate salts act as buffers.” Appx000039-000040. But the Board never returned to those deficiencies or found that Akorn disclosed the solution comprises sufficient phosphates to constitute a buffering agent to provide a pH of 4.8-6.0.

⁵ All bold italic emphases in quotations are added unless other indicated.

Instead, the Board concluded only that it was possible to use those same phosphate salts to provide some buffering capacity in some solutions. Appx000041 (“some buffering capacity may exist below or above” the buffering range), Appx000041 (“the pK_a for a buffer is not static, but depends on the parameters of the solution in which the buffer is used”); Appx000041-000042 (in some circumstances phosphate buffers’ “buffer range ... may be as low as pH 5.4”), Appx000043 (phosphate salts “able to buffer Akorn’s formulation at least in the upper part of the cited pH range.”). Next, the Board stated that a background reference regarding ophthalmic solutions generally recommended “the use of buffers to maintain the pH at the appropriate level” as required “to maintain shelf life.” Appx000044-000046. Finally, the Board found Akorn “disclose[d] a pH range of 3.5 to 6.0 for its formulation”—the USP-required pH limits for atropine sulfate ophthalmic solution. Appx000046 (citing Appx011232; Appx009675-009676). But the Board never found that Akorn disclosed using phosphate salts in amounts sufficient to constitute a buffering agent to provide a pH of 4.8 to 6.0.

When all was said and done, the Board found at most that Akorn listed ingredients that *could*, under certain circumstances, buffer at a USP-compliant solution pH. Importantly, the Board did not find that Akorn was buffered to maintain a pH of 4.8 to 6.0. It did not find that Akorn disclosed using the phosphates in the amounts necessary to buffer at a pH below 6.0. It did not even find that the Akorn

formulation was one to which the background reference's recommendation of a buffer would apply (i.e., it did not find that the Akorn formulation could not "maintain the pH at the appropriate level" or "maintain shelf life" without a buffer).

To the contrary, reading the Board's decision as a whole, its other findings demonstrate that Akorn's bare disclosure of phosphate inactive ingredients did not prove they were buffering at a pH between 4.8 and 6.0. Even though the Board reasoned that the "buffer range for [phosphates] *may* be as low as pH 5.4," it also found that the buffering range of an excipient "depend[s] on the conditions of the solution that is being buffered" and "depends on the parameters of the solution in which the buffer is used." Appx000041-000042. It was undisputed that those "conditions" and "parameters" (e.g., phosphate concentrations) are not disclosed in Akorn. Appx001282, Appx009693, Appx009827-009829, Appx009833. Thus, based on the Board's findings and undisputed facts, whether the phosphates as disclosed in Akorn buffered (controlled/maintained) at the indicated pH was unproven.

The Board's findings that buffering depended on variables not disclosed in Akorn were well supported. Sydnexis noted below that Petitioner did not meet its burden because Akorn "never discloses that the phosphate salts in its atropine solution ... were used in amounts sufficient to make a buffering agent," or "the actual pH of the disclosed solution." Appx010990-010991. Importantly, knowing the

amounts of the salts is critical to determining whether the weak acid is buffering (Appx008856, Appx008871, Appx009062, Appx009656, Appx009669-009670, Appx009691-009692, Appx009696-009697, Appx009824-009834). Petitioner never offered any evidence to the contrary. Nor did Petitioner dispute that the concentrations of phosphate salts in Akorn were undisclosed. Petitioner never introduced any evidence purporting to disclose the amounts of the phosphate salts in Akorn.

Petitioner also never disputed that the ability of a weak acid to buffer depended on the solution pH. For example, Petitioner's own pharmaceutical buffer reference asked, "When is a buffer not a buffer?," explaining that the answer is when the solution pH is outside ± 1 pH unit of the pK_a . Appx011212-011213 (citing Appx004054), Appx009637-009638. The very exhibit Petitioner's expert relied on for determining buffering ranges also identified phosphoric acid's pharmaceutical buffering range as having no overlap with the pH limitations in Akorn. Appx011213 (citing Appx004139 (Table 8), Appx009853-009854). In other words, the effective pharmaceutical buffering range for phosphates lay outside Akorn's required solution pH limits.

The potential that phosphate salts *might*—under some conditions not disclosed in Akorn—*be able to* act as buffering agents is not enough to establish that Akorn discloses the claims' buffering limitations. Indeed, when assessing whether

the art sufficiently disclosed a claim limitation, this Court has held that “speculative and tentative disclosure of what ‘might’ or ‘may’ lead to [a claimed limitation] does not sufficiently direct or instruct one of skill in this art.” *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011); *see also PersonalWeb Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993 (Fed. Cir. 2017) (*PersonalWeb I*) (holding that the Board’s holding that a combination “*would have allowed for*” a certain outcome was “not enough”). The Board’s decisions thus cannot stand because Petitioner failed to meet its “burden to prove that all claimed limitations [we]re disclosed in the prior art.” *Par Pharm.*, 773 F.3d at 1194.

The Board neither found nor could have found that Akorn disclosed the buffering limitations inherently. In addition to no express finding to that effect, this Court’s precedent is clear that in the obviousness context, “[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.] ... Obviousness cannot be predicated on what is unknown.” *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (citing *In re Oelrich*, 666 F.2d 578, 581-82 (CCPA 1981); *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966)); *see PersonalWeb Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1381 (Fed. Cir. 2019) (*PersonalWeb II*) (explaining that even if the Board never mentions inherency, when its conclusion requires that a reference, “without saying so,” discloses a claim limitation, it must be “f[i]nd[ing] that [a reference] inherently teaches” the relevant

claim limitation); *LBT IP I LLC v. Apple Inc.*, No. 22-1613, 2023 WL 3914920, at *3 (Fed. Cir. June 9, 2023) (similar).

That is because “inherency in an obviousness analysis ... ‘may not be established by probabilities or possibilities.’” *Par Pharm.*, 773 F.3d at 1195 (citation omitted). For example, in *PersonalWeb II* this Court assessed whether the Board had erred in finding that a certain reference taught a “‘compared to a plurality of values’ limitation” and held that it had erred. 917 F.3d at 1382. This Court reasoned that “[w]hile it [wa]s possible that [the reference’s] system utilize[d]” a comparative lookup table, “mere possibility is not enough.” *Id.* So too here. The “mere possibility” that the phosphates might be able to buffer at a USP-compliant pH, under circumstances not disclosed in Akorn, “is not enough” to establish that Akorn disclosed the buffering agent limitation. *Id.*

Petitioner never established that every use of phosphate salts inevitably creates a buffering agent to provide a pH of 4.8-6.0. To the contrary, phosphate salts are used outside of their pharmaceutical buffering range as tonicity adjusting agents. Appx000180 (3:52-62), Appx000182 (7:60-67), Appx000200-000201 (44:54-67), Appx000226 (96:43-53), Appx008843, Appx008873, Appx009670, Appx009679-009680, Appx009684. Petitioner agreed. Appx011043 (citing Appx008873). Tellingly, Petitioner’s expert was careful to distinguish between disclosure of a buffer and simply listing excipients that might be used to buffer. When asked if

Akorn “uses a buffer to maintain a pH of 3.5 to 6,” he responded “[t]hat’s correct. Well, ... it discloses standard buffering agents.” Appx009834. Because phosphate salts have different uses that depend on their concentrations and solution pH, and because Akorn failed to disclose the information necessary to determine whether they were buffering in its solution, Petitioner’s case would not even have succeeded as an inherency case (though Petitioner never asserted inherency and the Board never found inherency). *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (citations omitted) (holding that inherent disclosure is not “established by probabilities or possibilities” that “[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient” (alterations in original)). The Board’s obviousness conclusions should therefore be set aside for failure to satisfy the applicable legal standards.

Ultimately, Eyenovia invited the Board’s prejudicial legal error by relying on impermissible hindsight. Eyenovia argued that Akorn’s disclosure of phosphates should satisfy the buffering elements at a pH lower than 6.0 because the challenged patents disclose that phosphates can satisfy the claimed range. Appx011042. The Board adopted this erroneous thinking that the patent’s disclosure that phosphate salts can be used to satisfy its claims somehow remedies the deficiencies of Akorn’s disclosure. Appx000044-000045. As this Court has explained, however, it is not enough that a reference “suggests the employment of the same materials ... that are

identified in the [challenged] patent.” *Sud-Chemie, Inc. v. Multisorb Techs., Inc.*, 554 F.3d 1001, 1006 (Fed. Cir. 2009). Instead, the “same general classes of materials” can have “quite different properties” depending on various other factors. *Id.* Thus, “look[ing] only to the classes of materials described in the patents” can lead to “incorrectly conclud[ing] that [a reference] teaches the same [limitation] as that claimed in the [challenged] patent.” *Id.* at 1008.⁶ Because Petitioner put forward nothing more than speculation to show that **Akorn’s** ophthalmic solution comprised a buffering agent to provide a pH of 4.8-6.0, it failed to meet *its* burden of proof. That failure is sufficient to foreclose a holding of obviousness under the ground presented in the petition.

Because the Board’s obviousness conclusion was predicated on mere possibilities rather than disclosure in Akorn of the buffering element, as alleged in the petition, the Board’s judgment should be at least vacated.

B. The Board erroneously shifted the burden of proof to Sydnexis.

Instead of analyzing the sufficiency of Petitioner’s evidence, the Board impermissibly shifted the burden to Sydnexis to prove impossibility. Specifically, the Board required Sydnexis to prove that phosphate salts ***could never*** buffer at pH 4.8 to 6.0. Appx000038-000046. Additionally, the Board faulted Sydnexis for failing

⁶ The claims here also differ from Akorn in that they depart from the upper pH limit imposed by the USP. Appx009683.

to prove a negative: that a POSA would never add a buffer instead of requiring Petitioner to prove that a POSA would have been motivated to do so. Appx000049-000050. That burden shifting is legal error. *Fanduel, Inc. v. Interactive Games LLC*, 966 F.3d 1334, 1341 (Fed. Cir. 2020) (citation omitted) (“[W]e soundly rejected the idea of shifting even the burden of *production* from the petitioner to the patent owner once the Board institutes an IPR where ‘the patentee’s position is that the patent challenger failed to meet *its* burden of proving obviousness.’”); cf. *SAS Inst., Inc. v. Iancu*, 138 S.Ct. 1348, 1353-57 (2018) (explaining that petitioner’s burden is to prove the ground as presented in the petition); *In re Leithem*, 661 F.3d 1316, 1320 (Fed. Cir. 2011) (explaining the standard for new grounds of rejection).

This Court has reversed the Board’s decision in a case analogous to this one. In *In re Magnum Oil Tools*, this Court explained that in an IPR proceeding, “no burden shifts from the patent challenger to the patentee.” 829 F.3d at 1376. That “is especially true where the only issues to be considered are what the prior art discloses, whether there would have been a motivation to combine the prior art, and whether that combination would render the patented claims obvious.” *Id.* As in *Magnum Oil*, here the “final written decision is replete with examples where, rather than require [Petitioner] to prove its assertion of obviousness, the Board improperly shifted the burden to [Sydnexis] to disprove obviousness.” *Id.* at 1378. For example, when

discussing whether Akorn disclosed the buffering agent limitation, the Board begins by describing each parties' arguments and testimony, then it states:

“We disagree with Dr. Laskar’s [(Sydnexis’s expert’s)] reliance solely on the Waterman reference as disclosing a buffering range for phosphate salts that “has no overlap with a solution pH of 3.5 to 6.0” and do not credit his conclusion [about how] a POSA would understand this lack of overlap Dr. Laskar’s statements ... are not sufficiently supported by record evidence.”

Appx000043-000044. Importantly, the Board does not couple these statements with any discussion of how Petitioner showed that Akorn disclosed the buffering agent limitation.

The Board’s statements reveal that the Board “incorrectly shift[ed] the burden of proof” by faulting Sydnexis for allegedly “fail[ing] to provide any evidence to support [its] view.” *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir. 2018). “But, it [wa]s [Petitioner’s] burden to present ... evidence that [Akorn ...] disclosed the [buffering agent limitation] to one of skill in the art.” *Id.*; see also *IPR Licensing, Inc. v. ZTE Corp.*, 685 F. App’x 933, 940 (Fed. Cir. 2017) (deciding that the Board’s statement that “Patent Owner has advanced no evidence” showing that a reference did not disclose a limitation “seem[ed] to shift the burden of proof”). Sydnexis had no burden to prove that phosphate salts were incapable of acting as buffers in Akorn.

As in *Magnum Oil*, “the Board improperly assumed, without deciding, that ‘[Petitioner’s] position that [Akorn] teach[es] the claimed [buffering agent limitation]’ [wa]s correct” and “then required the patentee, [Sydnexis], to rebut the position of the petitioner ... and to prove nonobviousness of the claimed invention.” 829 F.3d at 1378. That improper burden shifting defies both statute and precedent. *Id.* at 1375-77; 35 U.S.C. §316(e). Accordingly, the Board’s decision should be set aside.

III. The Board prejudicially applied an improper legal standard in determining motivation to combine.

Even if prior art disclosure of all elements in the ground references is established, a petitioner still must prove that “a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have a reasonable expectation of success.” *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). This means that the Board must explain why a POSA would have taken the claim limitations disclosed in the grounds references and been motivated to combine them. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006); *see also Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (quoting *InTouch Techs., Inc. v. VGo Commc’ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014)) (“The obviousness inquiry does not merely ask whether a skilled artisan could combine the references, but instead asks whether ‘they would have been motivated to do so.’”). Otherwise a

challenger could “simply ... engage in a hindsight reconstruction of the claimed invention, using the applicant’s structure as a template and selecting elements from references to fill the gaps.” *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991).

Because it focused on what was *possible* rather than what a POSA *would have done* based on the available knowledge, the Board erroneously disregarded undisputed evidence that Sydnexis had discovered an unknown problem with the stability of low-concentration atropine solutions. The Board’s motivation to modify analysis was thus impermissibly infected by hindsight bias and should be set aside.

A. The Board erroneously disregarded Sydnexis’s discovery of an unknown or unexpected problem.

The Board erroneously failed to analyze obviousness in light of Sydnexis’s discovery of an unknown problem. That failure was a legal error and tainted the Board’s motivation analysis with improper hindsight. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354-55 (Fed. Cir. 2013). When “there [i]s no prior recognition of the problem solved by the subject invention, there [i]s no reason in the record why one of skill in the art would attempt to combine the cited prior art to arrive at the claimed invention.” *Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1338 (Fed. Cir. 2016), *overruled on other grounds by Aqua Prod., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017) (citing *Leo*, 726 F.3d 1346 at 1354); *see Forest Lab’ys, LLC v. Sigmapharm Lab’ys, LLC*, 918 F.3d 928, 935 (Fed. Cir. 2019) (citation omitted) (“We have recognized that where a problem was not known in the art, the solution to that

problem may not be obvious, because ‘ordinary artisans would not have thought to try at all because they would not have recognized the problem.’”). Thus, when assessing motivation in an obviousness analysis, it is legal error to “brush[] aside” that an unknown problem was solved. *Leo Pharm.*, 726 F.3d at 1354.

Here, the Board did just that. Sydnexis highlighted the problem to the Board, stating that “the challenged patent recognizes an unknown stability problem for low-concentration atropine solutions” and that the inventors “discovered that atropine degraded in aqueous solution at a faster rate when the atropine concentration was very low than when the atropine concentration was higher,” which was not disclosed in the prior art. Appx010975-010978, Appx010987, Appx011009-011010, Appx011060-011062. Sydnexis emphasized the importance of that problem, explaining that before “[t]he inventors discovered that low-concentration atropine suffered from a previously-unknown stability problem,” “adding a buffering agent to provide the acidic solution pH of storage” would be “without any expected stability benefit for atropine.” Appx010987-010988. And Sydnexis even cautioned the Board that assuming that the instability problem solved by the challenged patent was “part of the prior art” was “impermissible” “hindsight-driven reasoning.” Appx011009-011010; *see also* Appx010987-010988.

But the Board still “brush[ed] aside” Sydnexis’s discovery of the unknown instability problem (*see Leo Pharm.*, 726 F.3d at 1354), and concluded that a POSA

would have been motivated to add a buffer to low-concentration atropine solutions to “provide[] optimal patient compliance and clinical efficacy” while “remain[ing] stable over long periods of time.” Appx000050. To reach that conclusion, the Board used the challenged patents to identify the motivation to modify, which “represents a form of prohibited reliance on hindsight.” *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012).

Without the challenged patents, it is undisputed that the prior art taught that unbuffered atropine solutions were shelf-stable at the pH of 5-6 identified by the Petition as preferred for balancing stability with patient comfort. Appx010745, Appx009715-009716, Appx009813-009815, Appx009917-009918. Indeed, the very ground reference (Kondritzer) that Petitioner relied upon to establish the relationship between pH and atropine stability reports that the half-life of atropine at room temperature is 1800 years, 811 years, 266 years, and 27 years at pH 4.0, 4.5, 5.0, and 6.0, respectively. Appx001288 (Table III). It was unrebutted below that atropine was thus expected to have a stable shelf-life of several years without the use of a buffer even at a pH of 6.0. Appx009718-009720.

Even the Petition declares that the problem was “acidic values *at the lower end of* [pH 3-5 that] were known to cause patient discomfort and irritation.” Appx010741. Both parties agreed that the prior art taught that an atropine solution at pH 5 was stable without a buffer. Appx009715-009716, Appx009813-009815,

Appx009917-009918. Neither Petitioner nor the Board pointed to any shelf-life problem with an atropine solution at pH 5. Indeed, all of the evidence pointed the other way. Appx010968-010969 (collecting sources), Appx010987-010988, Appx009705-009709, Appx009716-009718, Appx009729-009730, Appx011205-011206, Appx009838-009843. Because no evidence shows an unbuffered solution at pH 5 was unstable or caused patient discomfort or non-compliance, there was no legal basis for finding motivation to modify Chia's formulation by adding a buffer.

Indeed, Petitioner conceded that Chia's low-concentration atropine solution was "stable." Appx010739. Nothing in Petitioner's evidence suggested that Chia's solution had any shelf-life issues despite being unbuffered. Consistent with this, all of the low-concentration atropine references Petitioner submitted disclosed using an unbuffered solution. For example, these references repeatedly disclose diluting higher concentration atropine solutions with distilled water or saline rather than buffering them. *See, e.g.*, Appx001345-001348, Appx001364, Appx001366-001367, Appx001383-001384. Petitioner's expert, Dr. Byrn, readily concede[d] that neither distilled water nor saline is a buffer despite having some buffering capacity (Appx009838, Appx009841, Appx009845), and that these low-concentration atropine references did not disclose the use of any buffer or buffering agent. *See, e.g.*, Appx011205-011206, Appx009838-009843. Sydnexis's expert agreed, observing that the low-concentration atropine ophthalmic art uniformly teaches

using an unbuffered solution. Appx009704-009708. Because the art “d[id] not suggest any need to stabilize [atropine solutions] beyond” adjusting the pH of the unbuffered solution down to pH 5-6 (e.g., using sodium hydroxide as taught in Akorn), a POSA “would not have seen any need to apply” to Chia Akorn’s alleged buffering systems. *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380 (Fed. Cir. 2008).

This Court’s decision in *Leo Pharmaceutical* is instructive. There (as here), “inventors ... recognized and solved a problem with the storage stability of certain formulations.” 726 F.3d at 1353. There (as here), “[t]o discover this problem, the ordinary artisan [had] to spend several months running storage stability tests.” *Id.* at 1354; *see also* Appx010977. There, this Court held that because the prior art “neither ... recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon [the prior art] using [another reference].” *Leo Pharm.*, 726 F.3d at 1354. Instead, a POSA “would first have needed to recognize the problem, i.e., that the formulations disclosed in [the prior art] were not storage stable.” *Id.* And “[o]nly after recognizing the existence of the problem would an artisan *then* turn to the prior art and attempt to develop a new formulation for storage stability.” *Id.* So too here. By ignoring the previously unknown stability issue with low-concentration atropine solutions

compared to higher-concentration atropine solutions, the Board applied the wrong motivation analysis and tainted its reasoning with hindsight.

Novartis Pharmaceuticals Corp. v. Watson Laboratories, Inc., 611 F. App'x 988 (Fed. Cir. 2015) is also instructive. In that case, this Court upheld the district court's conclusion that because "degradation was not a known problem," a POSA "would not have expected that an antioxidant was required" and thus "no motivation existed for adding an antioxidant." *Novartis Pharms.*, 611 F. App'x at 995. This was true even though one prior art reference *did* suggest adding antioxidants "as required." *Id.* at 996. Per this Court, "[w]ithout prior knowledge as to whether a compound is susceptible to oxidative degradation, the statement that excipients like antioxidants can be incorporated 'as required' is a mere generic qualification." *Id.* The same reasoning applies here. Because it erroneously disregarded that there "was not a known problem" with stability of atropine solutions at pH 5-6, the Board failed to realize that "no motivation existed for adding a" buffer. Generic statements in a background reference that buffers should be used "as required" to "maintain the pH at the appropriate level" only provide a motivation to combine if one first uses impermissible hindsight to assume buffering was "required."

The Board mentioned Sydnexis's discovery once: "regardless of whether the problem of the stability of atropine at low doses was unexpected, ... [t]he buffer [wa]s just doing exactly what a buffer does as recognized: *viz.*, maintaining pH."

Appx000047. But assuming a solution was obvious for an unknown problem is the very definition of impermissible hindsight. *Mintz*, 679 F.3d at 1377 (“when someone is presented with the identical problem and told to make the patented invention, it often becomes virtually certain that the artisan will succeed in making the invention”); *Novartis Pharms.*, 611 F. App’x at 995 (“Even an obvious solution, however, does not render an invention obvious if the problem solved was previously unknown.”). For instance, in *Novartis*, this Court held that “[a]lthough the addition of an antioxidant would have been an obvious solution for a formulation with known [degradation] problems,” “[w]ithout the knowledge of a problem,” a POSA “would not have been motivated to modify [a reference] with antioxidants.” 611 F. App’x at 996.

In other words, what matters here is whether a POSA “at the time of the invention would have recognized the [stability] problem recognized by the inventors,” or another problem that would have been solved the same way, “and found it obvious to [add the buffering agent] disclosed in the [challenged] patent to solve that problem.” *Mintz*, 679 F.3d at 1377-78; *ZTE Corp.*, 685 F. App’x at 940 (faulting the Board for reaching its conclusion based on “a statement about what skilled artisans could have done if motivated, not what they would have been motivated to do” because “[p]roof of the latter is needed”). Recognition of the problem is especially important in cases where incorporating the claimed limitation

“involve[s] tradeoffs,” such as between stability and patient comfort in this case. *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019). Here, “[b]y brushing aside the storage stability issue, the Board erred by collapsing the obviousness analysis into a hindsight-guided combination of elements.” *Leo Pharm.*, 726 F.3d at 1354. Indeed, adding a buffer to address the unknown stability issues with low-concentration atropine solutions “is only straightforward in hindsight.” *Id.* at 1355.

By deciding that it did not matter whether Sydnexis “discovered ... the problem of the stability of atropine at low doses,” the Board engaged in an improper, hindsight-driven analysis that must be set aside.

B. The Board erroneously shifted the burden of proof to Sydnexis.

The Board’s legal error for motivation to combine was compounded by the same erroneous burden shifting as before. Again, the Board begins by describing each side’s arguments. Appx000048-000049. The Board then focuses on Sydnexis’s arguments. It first references its conclusion that Sydnexis’s view of the state of the art was “not sufficiently supported by record evidence.” Appx000044. Next, it turns to Sydnexis’s argument that “adding a buffer would decrease patient comfort,” stating that it “d[id] not find this argument persuasive.” Appx000049. Only then does it assess Petitioner’s arguments for motivation. And its entire analysis states:

We agree with Petitioner and Dr. Byrn that “a POSA would have been motivated to formulate low-concentration atropine solutions that could

be administered at pHs closer to those that provided optimal patient compliance and clinical efficacy, but that could also remain stable over long periods of time.” We determine that Petitioner has shown an appropriate reason to combine the teachings of Chia, Akorn, and Kondritzer to arrive at the composition of claim 1 with a reasonable expectation of success.

Appx000050 (internal citations omitted). Effectively, the Board held that Sydnexis had not proven that a POSA would be discouraged from adding a buffer and then without further analysis held that a POSA would have been motivated to do so. This type of reasoning is impermissible. *See Magnum Oil*, 829 F.3d at 1380 (“cannot employ mere conclusory statements.” (citing *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007))); *Kahn*, 441 F.3d at 986 (citation omitted) (“When the Board does not explain the motivation, or the suggestion or teaching, that would have led the skilled artisan at the time of the invention to the claimed combination as a whole, we infer that the Board used hindsight to conclude that the invention was obvious.”). The Board’s language, its focus on rebutting Sydnexis’s arguments instead of assessing Petitioner’s evidence, and the dearth of findings as to Petitioner’s showing of obviousness all reveal that the Board improperly shifted the burden from Petitioner to Sydnexis. *Magnum Oil*, 829 F.3d at 1376.

The lack of evidence for motivation makes the Board’s shifting of the burden even more evident: the Board’s generic finding on motivation to combine (that a POSA would want the solution to be both stable and comfortable) does not speak to

the most crucial question: would a POSA have been motivated to modify Chia's unbuffered, low-concentration atropine solution by adding a buffering agent to provide a pH of 4.8 to 6.0, as alleged in the petition? Without a predicate finding that the prior art taught that unbuffered low-concentration atropine solutions were unstable at the comfortable pH of 5-6 proposed by the Petition (*see* Section III.A), the Board's finding as to motivation is missing a crucial link to show obviousness. *Star Sci.*, 655 F.3d at 1376-77 (holding that a combination "d[id] not provide a link between ... critical targets of the [challenged] patents").

At most, the Board concluded that a POSA *could* have added a buffer if needed to increase stability, "not that [a POSA] *would* have been motivated to do so." *InTouch Techs.*, 751 F.3d at 1352 (citing *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012)). But "that is not the relevant inquiry." *Id.* "[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Because the "analysis was incomplete," it is "ultimately insufficient to establish obviousness." *InTouch Techs.*, 751 F.3d at 1352; *PersonalWeb I*, 848 F.3d at 993-94 ("[T]hat reasoning seems to say no more than that a skilled artisan ... would have understood that [references] *could be* combined.

And that is not enough: it does not imply a motivation to pick out those two references and combine them to arrive at the claimed invention.”).

IV. The Board’s buffer findings prejudicially lack substantial evidence.

A. No substantial evidence supports buffering Chia’s low-concentration atropine solution at a pH of 5-6.

The Board identified a general recommendation in the art to use buffers in ophthalmic solutions when needed to maintain pH “at the appropriate level” for adequate shelf life, while avoiding excess buffer capacity to facilitate “patient comfort and compliance.” Appx000045-000046 (citing Appx001176). The Board concluded that adding a buffer to an unbuffered atropine ophthalmic solution would not decrease patient comfort because a POSA would minimize the buffering capacity so that it was just high enough to “balance the shelf-life of the solution with a buffering capacity that allows a patient’s tears to easily overcome an uncomfortable acidic pH of the ophthalmic solution.” Appx000049-000050 (citing Appx001461). In other words, the Board reasoned that any buffering employed for an atropine solution would be minimized to what was necessary to maintain shelf life to avoid causing patient discomfort. But this was exactly Sydnexis’s point: Petitioner never demonstrated buffering was necessary to maintain shelf life and avoid patient discomfort. Without evidence of instability, there was no motivation to add buffering.

One background reference teaches that when a solution is buffered such that the solution “resist[s] adjustment by tear fluid and the overall eye pH remains acid

for an appreciable period of time, then stinging and discomfort may result.” Appx001461. In other words, a buffer that maintains acidic solution pH and resists reestablishment of native tear pH actually increases patient discomfort. Appx009675-009678, Appx009679-009681, Appx009684-009689, Appx009709-009710. Another reference teaches that “pH has little effect on comfort if the solution is unbuffered” and that the “major determinant” for eye discomfort is “the buffering capacity of the solution rather than the specific pH.” Appx001905, Appx001908; *see also* Appx008852, Appx008888. Accordingly, adding buffering to an acidic ophthalmic solution was not a default approach; it was undertaken only when it was known to be needed for stability. Appx009717 (citing Appx011241-011242) (mantra of ophthalmic formulator not to add unnecessary ingredients).

The Board acknowledged that Petitioner’s low-concentration atropine references disclosed unbuffered solutions but dismissed that fact because some were “studies to determine the safety and efficacy of low-dose atropine solutions and were not commercially available formulations that must meet FDA requirements for safety and efficacy.” Appx000049. But there was no evidence that unbuffered atropine solutions were unstable or unfit for FDA requirements for safety and efficacy. Indeed, Chia’s unbuffered atropine solution was obtained from a commercial source. Appx001273 (Ashwood Laboratories, Ltd). And everyone agrees that Chia reports its solution was safe and effective. Appx010721-010722,

Appx010968, Appx001279. In fact, Petitioner argued below that Chia's solution "reduced patient compliance problems" and was a "clinical success." Appx010737. But no one disputed that Chia's solution was unbuffered. Appx009705-009706, Appx009708-009709, Appx009716-009718, Appx009729-009730 (describing its unbuffered low-concentration atropine solution as "a safe and effective regimen"). Accordingly, the Board's rationale for disregarding the prior-art teaching to employ unbuffered ophthalmic atropine solutions lacks substantial evidence.

None of the petition's low-concentration atropine references discloses using a buffering agent to provide a pH of 4.8 to 6.0. Instead, many of them were diluted with unbuffered water. Appx011205-011206, Appx001345-001348, Appx001364, Appx001366-001367, Appx001383-001384, Appx001192-001194, Appx009838-009843.

When storage stability was desired, strong acid or base were used to adjust the solution pH below 6.0 where atropine was known to be stable. Appx009715-009716 ("[A]tropine stability was achieved without using a buffering agent to provide the pH."). Petitioner's expert repeatedly agreed. For example, he testified that a "POSA would balance [stability and patient comfort] by *adjusting* the solution pH to the higher end of the pH range of 2 to 5.4." Appx009918; *see also* Appx009930-009931 (testifying that a POSA "would *adjust* a solution pH ... for optimum drug stability"). He testified that atropine was believed to be very stable

at acidic storage pH without using buffering. Appx009917 (agreeing that low-concentration atropine solutions would “remain stable at the higher end of [pH 2 to 5.4] while increasing patient comfort”), Appx009718-009721, Appx009730-009731, Appx009734-009735. And Petitioner argued below that storage stability was inherent to atropine adjusted to acidic storage pH. Appx010993-010994, Appx010748 (“*Kondritzer* taught that atropine in aqueous solutions had a half-life measured in *years*.” (emphasis in original)). Because it failed to consider that adjusting the solution pH to 5-6 with hydrochloric acid or sodium hydroxide (just as disclosed in Akorn) provided stability with minimum discomfort, the Board’s generic conclusion that there was a desire for adequate stability and comfort does not establish a motivation to add buffering.

B. Substantial evidence does not support the Board’s departure from the pharmaceutical buffering range of phosphate salts.

The Board found that phosphate salts might buffer in some solutions having a pH as low as 5.4. Appx000041-000042. But substantial evidence does not support a holding that departing from the pharmaceutical buffering range of phosphate salts satisfies the buffering limitations of the claims. As Sydnexis explained below, the very reference Petitioner’s expert relied upon to explain buffering states: “Buffers are most effective within ± 1 pH unit from their pK_a . Outside of that range the concentration of either the acid or its salt is so low as to provide *little to no capacity for pH control*.” Appx004054. When the solution “provide[s] little or no capacity

for pH control[] [t]hat ... is the definition of an ineffective buffer” and “[i]f a buffer doesn’t act like a buffer, it’s not a buffer.” Appx008843-008845, Appx004054 (“When is a buffer not a buffer?”). All parties agreed the claims use the ordinary meaning of “buffer” (Appx010736, Appx010985-010986, Appx011041), not an ineffective or nonfunctioning buffer (Appx000013-000014).

In explaining how to calculate effective pharmaceutical buffering ranges, Petitioner’s expert relied on the Waterman reference. Appx011213 (citing Appx004139). The Waterman reference discloses that the pK_a of phosphates is 7.2 and—using the ± 1 pH unit calculation—the effective pharmaceutical buffer range is 6.2-8.2. Appx004139 (Table 8). Thus, according to the Petitioner’s expert’s declaration, effective buffering of phosphate salts occurs entirely outside the USP pH limitations required in Akorn. A POSA thus would not have chosen to use phosphate salts to buffer the Akorn solution. Appx009681, Appx009694-009695.

The opinions of Petitioner’s expert—Dr. Byrn—that imply the contrary are wrong. On cross, Dr. Byrn admitted that his opinions were “premised” on using “a buffering range outside a plus or minus one” pH unit of the pK_a . Appx009870. A court has already considered and rejected that approach when considering Dr. Byrn’s opinions in another case. Appx010018-010022. Though the legal question was different in that case, the factual question about effective buffering was the same.

Importantly, there, as here, the scientific literature taught that buffering of a weak acid occurs ± 1 pH unit from the acid's pK_a . Appx009992-009993. There, as here, Dr. Byrn argued that a weak acid was a buffering agent in a specific solution because it “may provide buffering capacity,” even if the solution was outside the ± 1 pH unit “effective” buffering range of the acid. Appx010018-010019, Appx010022. The court rejected Dr. Byrn’s theory, holding instead that a salt could “[n]ot be a functioning buffer” because it “ha[d] pK_a s outside the pH range of ± 1 of the formulation, which would render it ineffective as a buffer.” Appx010045. The court found that “the effective pK_a range is ± 1 , not ± 2 as Dr. Byrn asserted,” and thus the pK_a of the weak acid must be within ± 1 pH unit of the product for a buffer to function properly. Appx009992-009993, Appx010018-010019, Appx010045. This was true even though the weak acid may provide some buffering capacity at the solution pH outside its buffering range. Appx010022, Appx010045.

In reply, Petitioner pointed to additional references addressing non-ophthalmic solutions to suggest that certain phosphate solutions can have a pK_a lower than 7.2 or a pH lower than 6.2. Appx011043-011044. But Dr. Byrn never asserted that the relevant pK_a s were different than the values in Waterman. Indeed, no expert relied on any of the reply references. Nor could any expert have relied on them: all of the reply references discuss “buffers” for biological assays, not ophthalmic formulations. Appx008943-009077. These reply references are

irrelevant for other reasons as well. One purposefully “adjust[ed]” the “final pH” of the phosphate solution down. Appx008856, Appx009048. Another reference notes that the pK_a of a particular acid varies depending on the concentration used. Appx001459, Appx008853, Appx009062, Appx009068, Appx009078; *see also* Appx008965-008967 (using significantly higher phosphate concentrations). The other references are likewise discussing phosphate solutions with no connection to ophthalmic formulations and that a POSA thus would not have looked to when formulating ophthalmic atropine. Appx008991-009023, Appx009078-009125. Petitioner did not show how any of these pK_a s for different solutions under different conditions were relevant to Akorn’s solution. Appx008869.

And even if the reply references were relevant, they contradict Petitioner’s argument. For example, one notes that the middle pK_a of phosphate is 7.21, that “[m]ost simple buffers work effectively in the scale of $pK_a \pm 1.0$,” and that even the biological buffering system that had a lower pK_a of 6.86 still only “provide[d] effective buffering in the pH range of 6.4 to 7.4.” Appx009036, Appx009038. In other words, adjusting the pK_a did not extend the buffering range. That reference also states that materials used to make buffers “will not exhibit any buffering capacity until the pH is adjusted” to be near the pK_a . Appx009045. The Board inexplicably disregarded these teachings, but relied on these references to conclude that phosphates might buffer at pH below 6.0 without any evidence that any of these

solutions described the composition of the solution in Akorn. Appx000041-000044. The Board’s selective reading of these references is not supported by substantial evidence. *Princeton Vanguard, LLC v. Frito-Lay N. Am., Inc.*, 786 F.3d 960, 970 (Fed. Cir. 2015) (“Just as it may not short-cut its legal analysis, the Board may not short-cut its consideration of the factual record before it.”).

CONCLUSION AND STATEMENT OF RELIEF SOUGHT

For the reasons discussed, the Board’s decisions should be reversed or at least be vacated and remanded.

Dated: February 1, 2024

/s/ Michael T. Rosato
Michael T. Rosato

*Counsel for Appellant Sydnexis,
Inc.*

Addendum

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EYENOVIA, INC.,
Petitioner,

v.

SYDNEXIS, INC.,
Patent Owner.

IPR2022-00384
Patent 10,842,787 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
Administrative Patent Judges.

MITCHELL, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Denying Patent Owner's Motion to Exclude
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

A. Background and Summary

On December 29, 2021, Eyenovia, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1, 2, 4–9, and 12–19 of U.S. Patent No. 10,842,787 B2 (Ex. 1001, “the ’787 patent”). Paper 1, (“Petition” or “Pet.”). Sydnexis, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition on April 18, 2022. Paper 6 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to the Preliminary Response addressing the public accessibility of Exhibit 1004¹ and Patent Owner’s proposed claim construction for “buffer” and “buffering agent.” *See* Ex. 3001; Paper 7. Also, with our authorization, Patent Owner filed a Sur-reply in response. *See* Ex. 3001; Paper 8.

On July 15, 2022, we granted institution of an *inter partes* review of claims 1, 2, 4–9, and 12–19 of the ’787 patent on all grounds set forth in the Petition. *See* Paper 9 (“Dec.”) 2, 41.

Patent Owner filed a Response on October 21, 2022, *see* Paper 19 (“PO Resp.”), and Petitioner filed a Reply on January 13, 2023, *see* Paper 21 (“Reply”). Patent Owner filed its Sur-Reply on February 24, 2023. Paper 24 (“Sur-Reply”). An oral hearing was held on April 14, 2023, and a transcript of this hearing was entered into the record. Paper 36 (“Tr.”).

Patent Owner filed a Motion to Exclude Evidence on March 24, 2023. Patent Owner seeks to exclude Exhibit 1002, the Declaration of Dr. Byrn, Petitioner’s declarant, Exs. 1004 and 1057 constituting the Akorn labels, and Exhibits 1079 through 1088, Eyenovia’s Reply exhibits. Paper 29.

¹ Atropine Sulfate Ophthalmic Solution, USP 1%, NDA 206289 Product Label (July 2014) (Ex. 1004, “Akorn”).

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Petitioner opposed the motion, *see* Paper 30, and Patent Owner filed a reply, *see* Paper 32. For the reasons set forth herein, the motion is *denied*.

This is a Final Written Decision under 35 U.S.C. § 318(a) as to the patentability of the challenged claims on which we instituted trial. Based on the complete record before us, we determine as set forth below that Petitioner has shown by a preponderance of the evidence that claims 1, 2, 4–9, and 12–19 of the ’787 patent are unpatentable.

B. Real Parties in Interest

The parties identify themselves as the real parties-in-interest. Pet. 63; Paper 4, 2; Paper 27, 2.

C. Related Matters

Petitioner asserts “[t]here are no other judicial proceedings that may affect or be affected by a decision in this proceeding.” Pet. 63. Petitioner further states that the ’787 patent issued from U.S. Application No. 15/568,381, a national phase application of International Application No. PCT/US2016/029222, which in turn is a continuation-in-part application of U.S. Application No. 14/726,139 that issued as U.S. Patent No. 9,421,199 (“the ’199 patent”). *Id.* at 63–64; *see also* Paper 11, 1 (Patent Owner provides a similar recitation of the ’787 patent’s history). According to Petitioner, the ’199 patent was challenged in IPR2021-00439 by Nevakar, Inc. *Id.* at 64. Petitioner states that IPR2021-00439 and other petitions filed by Nevakar, Inc. challenging Patent Owner’s patents were terminated due to settlement prior to institution. *Id.*; *see also* Paper 11, 2 (Patent Owner provides a similar recitation of the Nevakar proceedings).

Patent Owner identifies IPR2022-00414 and IPR2022-00415 as related matters. Paper 4, 2; Paper 27, 2. Patent Owner also states that it is

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the owner of the following United States patents related to the '787 patent: U.S. Patent No. 10,940,145; U.S. Patent No. 10,888,557; U.S. Patent No. 9,770,447; U.S. Patent No. 10,076,515; and U.S. Patent No. 10,201,534. Paper 11, 1–2. Patent Owner also identifies the following pending U.S. Applications related to the '787 patent: U.S. Application No. 17/097,930; U.S. Application No. 16/785,411; U.S. Application No. 16,908,426; U.S. Application No. 17,681,560; U.S. Application No. 17/721,838; and U.S. Application No. 17/721,831. *Id.* at 2.

D. The '787 Patent

The '787 patent relates to stabilized ophthalmic compositions comprising a muscarinic receptor antagonist for the treatment of an ophthalmic disorder, such as pre-myopia, myopia, or the progression of myopia. Ex. 1001, 5:4–8. Myopia is characterized by an axial elongation of the eye that begins during grade school years and progresses until growth of the eye is complete. *Id.* at 10:44–47. The Specification explains that muscarinic antagonists, such as atropine, prevent or arrest the development of myopia in humans. *Id.* at 9:50–56.

The Specification states that the clinical use of atropine for therapy had been limited due to side effects, such as glare from pupillary dilation and blurred vision. Ex. 1001, 12:21–24. The '787 patent attributes these effects to high concentrations of atropine (e.g., 1 wt % or higher). *Id.* at 12:24–29. The Specification explains also that some muscarinic antagonist compositions were formulated with lower pH values (e.g., less than 4.5) to promote stability of the muscarinic antagonist. *Id.* at 10:3–7. The lower pH values, however, cause discomfort or other side effects, such as pain or a burning sensation in the eye, which can be prevented or

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alleviated by formulating muscarinic antagonist compositions at higher pH ranges. *Id.* at 10:7–11.

According to the Specification, “there is a need for a stabilized ophthalmic composition with extended shelf life upon storage,” and there is a need for stabilizing such a composition by arresting or reducing hydrolysis of at least some of its active agents. Ex. 1001, 9:45–50. The Specification also recognizes that “there is a need for an ophthalmic composition that provides convenient and effective delivery of a muscarinic antagonist such as atropine in the eye of a patient.” *Id.* at 9:50–53. In view of this, the ’787 patent contemplates low concentrations of ophthalmic agents (e.g., from about 0.001 wt% to about 0.5 wt%). *Id.* at 12:30–35. For instance, the Specification describes ophthalmic compositions that include from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist, such as atropine or atropine sulfate, and water. *Id.* at 6:60–63, 7:1–2.

Additionally, the Specification describes pH values for the ophthalmic compositions (e.g., less than about 7.3, or less than about 6.4) after an extended period of time under storage condition. Ex. 1001, 7:9–16. The Specification also describes the compositions in terms of the concentration of the muscarinic antagonist based on initial concentration after an extended period of time under storage condition, and potency after an extended period of time under storage condition. *Id.* at 7:3–8, 17–21. The Specification describes “the extended period of time” as one having a duration of a range between about one week to about five years. *Id.* at 7:22–27. The storage condition is described for some embodiments as having a storage temperature of about 25° C, 40° C, or about 60° C, and in other embodiments from about 2° C to 10° C, or from about 16° C to about 26° C. *Id.* at 7:28–32.

The Specification explains that certain embodiments of the invention may further comprise additional agents, including, an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, a pH adjusting agent, and a pharmaceutically acceptable carrier. Ex. 1001, 7:43–8:39.

E. Illustrative Claims

Petitioner challenges claims 1, 2, 4–9, and 12–19 of the '787 patent. Claim 1 is the only independent claim. For this Final Written Decision, independent claim 1 (set forth below with bracketed letters to identify specific limitations for ease of reference) is illustrative of the claimed subject matter.

1. 1[a] A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising[:]

1[b] from about 0.001 wt% to about 0.05 wt% of atropine or atropine sulfate and water, wherein

1[c] the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein the

1[d] stabilized ophthalmic composition is a liquid, and wherein

1[e] the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.

Ex. 1001, 97:32–44 (bracketing, labels, and formatting added).

Dependent claims 2, 4–9, and 12–15 provide additional limitations to further refine the stabilized ophthalmic compositions of claim 1. *See* Ex. 1001, 97:45–48, 97:51–98:17, 98:25–41. Dependent claim 16 recites

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that the stabilized ophthalmic composition of claim 1 is topically administered. *See id.* at 98:42–44. Dependent claim 17 recites that the stabilized ophthalmic composition of claim 1 is administered by instillation. *See id.* at 98:45–47. Dependent claim 18 recites that the stabilized ophthalmic composition of claim 1 is administered through an eye drop bottle. *See id.* at 98:48–51. Claim 19 recites a method of treating the pre-myopia, myopia, or progression of myopia by administering an effective amount of the stabilized ophthalmic composition of claim 1. *See id.* at 98:52–56.

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 1, 2, 4–9, and 12–19 would have been unpatentable on the following grounds:

Claims Challenged	35 U.S.C. §²	Reference(s)/Basis
1, 2, 4–9, 12–19	103	Chia, ³ Akorn, ⁴ Kondritzer ⁵
1, 2, 4–9, 12–19	103	Chia, Akorn, Lund ⁶

² The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the ’787 patent issued has an effective filing date after that date, the AIA version of § 103 applies.

³ Audrey Chia et al., *Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)*, 119 OPTHALMOLOGY 347–354 (2012) (Ex. 1003, “Chia”).

⁴ Atropine Sulfate Ophthalmic Solution, USP 1%, NDA 206289 Product Label (July 2014) (Ex. 1004, “Akorn”).

⁵ Albert A. Kondritzer & Peter Zvirblis, *Stability of Atropine in Aqueous Solution*, 46 J. AM. PHARM. ASSOC. 531–535 (1957) (Ex. 1005, “Kondritzer”).

⁶ Walter Lund & Tor Waaler, *The Kinetics of Atropine and Apotatropine in Aqueous Solutions*, 22 ACTA CHEM. SCAND. 3085–97 (1968) (Ex. 1007, “Lund”).

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Claims Challenged	35 U.S.C. § ²	Reference(s)/Basis
1, 2, 4–9, 12–19	103	Akorn, Wu, ⁷ Kondritzer

Petitioner also relies upon the Declaration of Stephen Byrn, Ph.D. (Ex. 1002). Patent Owner relies upon the Declaration of Paul A. Laskar, Ph.D. (Ex. 2003).

II. ANALYSIS

A. *Principles of Law*

1. *Burden*

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016 (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”))). Therefore, in an *inter partes* review, the burden of proof is on the Petitioner to show that the challenged claims are unpatentable, and that burden never shifts to the patentee. *See* 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).

⁷ WO 2014/182620 A1, published November 13, 2014 (Ex. 1006, “Wu”).

2. Obviousness

To ultimately prevail in its challenge to Patent Owner’s claims, Petitioner must demonstrate by a preponderance of the evidence⁸ that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains (“POSA” or “POSITA”). *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In determining obviousness when all elements of a claim are found in various pieces of prior art, “the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success.” *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also WMS Gaming, Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) (“When an obviousness determination relies on the combination

⁸ The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

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of two or more references, there must be some suggestion or motivation to combine the references.”). “Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 1381, 1381 (finding a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.”) (internal quotations and citations omitted).

An obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. Section 103 “bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. *KSR*, 550 U.S. at 399 (stating that obviousness is determined against the backdrop of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the art). Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner asserts that “[a] person of ordinary skill in the art (‘POSA’) at the time of the purported invention would have had a Ph.D. in chemistry, organic chemistry, physical chemistry, or pharmaceuticals, with several years of experience preparing and/or testing pharmaceutical formulations.” Pet. 21–22 (citing Ex. 1002 ¶ 62). Petitioner further contends that “[a] POSA would have been familiar with common inactive ingredients used in aqueous pharmaceutical formulations and the basic characteristics of aqueous formulations such as stability, and would have had knowledge about drug degradation kinetics.” *Id.* at 22.

Patent Owner asserts that a narrower definition of a POSA should be employed—one that includes expertise in ophthalmic formulation. PO Resp.

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4.⁹ Patent Owner states that Petitioner’s declarant, Dr. Byrn, has “extremely limited experience with ophthalmic formulation,” which “calls into serious question whether he is qualified to opine on the perspective of a POSA in the relevant field.” *Id.* at 5.

We do not agree with Patent Owner that the level of ordinary skill in the art should be limited to experience with ophthalmic formulation. The claims at issue generally require a liquid ophthalmic formulation of a small amount of atropine that is stabilized using buffers that can be stored for at least two weeks under certain temperature and humidity conditions. *See* Ex. 1001, 97:32–44 (claim 1). As Dr. Byrn points out, the technology surrounding use of atropine, a nonselective muscarinic antagonist, to treat myopia, has been extensively studied for over a hundred years and is known as “the oldest and most effective pharmacological treatment to inhibit the development of myopia.” *See* Ex. 1002 ¶ 26 (quoting Ex. 1008, 1) (citing Ex. 1003, 1; Ex. 1012, 2). The degradation of atropine is also well known to primarily result from cleavage of the acyl-oxygen bond during ester hydrolysis, *see id.* ¶ 43 (citing Ex. 1017, 1; Ex. 1024, 5), with the rate of acid-catalyzed reaction being much slower than that of the base-catalyzed reaction, leading to stability of atropine at a lower pH range (pH < ~3), *see id.* ¶ 45 (citing Ex. 1005, 1,4–5). Concerning specifically the use of atropine in the eye, Dr. Byrn points out that it is well known that ophthalmic solutions should be “formulated to be sterile, isotonic and buffered for stability and comfort.” *See id.* ¶ 47 (quoting Ex. 1019, 52) (noting Ex. 1019, 54 (pH of tear fluid is 7.4)).

⁹ Although Patent Owner disagrees with Petitioner’s definition of a POSA, Patent Owner does not provide its own definition apart from including expertise in ophthalmic formulation. *See* PO Resp. 4–7.

None of this chemistry concerning the stability of atropine or its administration in the eye is remarkable or not well understood by a POSA as defined by Petitioner. *See* PO Resp. 10 (stating “the stability of atropine was understood to be a ‘predictable function,’ and a ‘routine matter,’ of temperature and solution pH”), 43–44 (same). We see no reason why someone with drug formulation experience, but not specific experience with ophthalmic solutions, would not qualify as a POSA. Therefore, we continue to apply Petitioner’s definition of a POSA in this final written decision.

C. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 100(b) (2019). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioner states that “[f]or the purposes of this proceeding only, Petitioner does not believe that any claim terms need to be construed.” Pet. 22. Patent Owner “agrees that the claims should be understood according to their ordinary and customary meaning.” PO Resp. 25–26. In reply, Petitioner asserts that the ordinary meaning of “about” is

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“approximately,” and the ordinary meaning of “buffering agent” or “buffer” “is nothing more than an excipient that helps control pH.” Reply 2.

Petitioner asserts that Patent Owner agrees with the definition of “buffering agent” and “buffer” by stating that “[t]he patent uses terms buffer and buffering in their normal sense, which entails providing pH control or maintenance.” *Id.* (quoting PO Resp. 29).

Based upon our review of the evidence of record, we determine that no claim terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (Only those terms that are in controversy need be construed, “and only to the extent necessary to resolve the controversy.”). Insofar as the parties dispute whether Akorn discloses a buffer, we address those contentions in our discussion below of the challenged claims.

D. Obviousness over Chia, Akorn, and Kondritzer

Petitioner asserts that claims 1, 2, 4–9, and 12–19 would have been obvious over the combined teachings of Chia, Akorn, and Kondritzer. Pet. 23–42. In addition to challenging the public availability of Akorn, Patent Owner disagrees with the substance of Petitioner’s argument and states that the Akorn reference “does not disclose the phosphate salts are buffering agents. Nor does it disclose that the Akorn product has a pH range of 3.5–6.0. Each of these failures is case-dispositive.” PO Resp. 1.

1. Chia (Ex. 1003)

Chia is a journal article that describes two studies regarding the treatment of myopia using atropine eyedrops. Ex. 1003, 1. In the first study, Atropine for the Treatment of Myopia 1 (“ATOM1”), it was shown that atropine 1% eyedrops were effective in controlling myopic progression but

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with visual side effects resulting from cycloplegia and mydriasis. *Id.* The second study described in Chia, Atropine for the Treatment of Myopia 2 (“ATOM2”), compared the efficacy and visual side effects of 3 lower doses of atropine: 0.5%, 0.1%, and 0.01%. *Id.* The authors of Chia conclude “[a]tropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression.” *Id.*

Chia notes that atropine, a nonspecific muscarinic antagonist, at 1.0% and 0.5% has been shown to be effective in slowing myopia progression, but its safety profile regarding pupil size and accommodation was a concern.

Ex. 1003, 6. Chia states:

Every unit increase in pupil size results in an exponential increase in the amount of light entering the eye, and this can cause glare and potential phototoxicity. Atropine also decreases accommodation amplitude and near vision so that children may require bifocal or progressive glasses to read. The ideal atropine dose would be one with the best balance between efficacy and safety.

Id.

To explore the ideal atropine dose, Chia performed the ATOM2 study using 0.01% atropine as a potential control due to its assumed minimal effect. Ex. 1003, 7. Chia found that “contrary to expectations, atropine 0.01% also had significant clinical effects as evidence by its effect on myopia progression, accommodation, and pupil size.” *Id.* In comparing the 0.01% atropine dose to the 0.5% and the 0.1% doses, Chia found “the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared with the 0.5% group. Likewise, the difference in axial length increase was statistically larger than in both the 0.1% and 0.5% groups. However, absolute differences between groups were

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clinically small” *Id.* Chia did note that no other atropine 0.01% studies were available for direct comparison, but Chia did compare the data to a study¹⁰ testing 0.05% atropine and a study¹¹ testing 0.025% atropine. *Id.*

Although Chia found that “[o]verall, atropine-related adverse effects were uncommon at the 0.01% dose . . . [t]here are no long-term studies on the effect of atropine on the eye, and continued vigilance is necessary. However, atropine has been clinically available since the early 1900s, and so far there are no known long-term adverse effects associated with its use.” Ex. 1003, 7. Chia states:

In conclusion, our results suggest that 0.5%, 0.1%, and 0.01% atropine remain effective in reducing myopia progression, compared with placebo treatment, and that the clinical differences in myopia progression among these 3 groups are small. The lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while attaining a clinically significant improved safety profile in terms of accommodation, pupil size, and near visual acuity, and subsequently reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer adverse events. Atropine 0.01% is currently not commercially available. However, these findings collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.

Id. at 7–8.

¹⁰ Jong-Jer Lee et al., *Prevention of myopia progression with 0.05% atropine solution*, 22 J. OCU. PHARMACOL. & THER. 41–46 (2006) (Ex. 1012, “Lee”).

¹¹ Fang et al., *Prevention of myopia onset with 0.025% atropine in premyopic children*, 26 J. OCU. PHARMACOL. & THER. 341–45 (2010) (Ex. 1013, “Fang”).

2. *Akorn (Ex. 1004)*

Petitioner identifies Ex. 1004 as a product label for Akorn Atropine Care, which appears to be an excerpt from New Drug Application 206289. *See* Pet. vii; Ex. 1004, 1. Akorn describes a 1% atropine sulfate ophthalmic solution for topical application to the eye. Ex. 1004, 1. Akorn explains that atropine is an anti-muscarinic agent that is indicated for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia. *Id.* at 1, 2. Akorn explains atropine's mechanism of action as follows:

The pupillary constrictor muscle depends on muscarinic cholinergic activation. This activation is blocked by topical atropine resulting in unopposed sympathetic dilator activity and mydriasis. Atropine also weakens the contraction of the ciliary muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate such that the eye cannot focus for near vision.

Id. at 4. Akorn describes applying 1 drop of the solution to the cul-de-sac of the conjunctiva forty minutes prior to an intended maximum dilation time. *Id.*

Akorn explains that the solution contains atropine sulfate as an active ingredient. Ex. 1004, 3. Akorn further describes the following inactive ingredients: "benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP." *Id.*

3. *Kondritzer (Ex. 1005)*

Kondritzer is a journal article that relates to a kinetic study of the proton catalyzed hydrolysis of atropine "to identify and evaluate the factors involved in the deterioration of aqueous solutions of atropine and its salts," and confirmed the temperature dependency of the reaction. Ex. 1005, 1.

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Kondritzer explains that the alkaline hydrolysis of atropine in aqueous solution involves two reactions: “one involving the unprotonated (base) form, and the other the protonated (ionic) form of the alkaloid,” with each reaction being governed by hydroxyl-concentration and temperature. *Id.* Kondritzer also notes some previous work concerning the stability of aqueous atropine solutions stating: “The preservation of aqueous atropine solutions by buffering at pH 4-5 has been recommended.” *Id.* at 2.

Kondritzer’s evaluation included studying the hydrolysis of atropine in various perchloric acid solutions at temperatures varying from 70° C to 90° C. Ex. 1005, 2. Based on this, Kondritzer prepared an equation to predict the rate of proton hydrolysis at any particular temperature and hydrogen ion concentration. *Id.* Kondritzer takes into account the effect of both hydroxyl and hydrogen ions to determine the pH of minimum hydrolysis at various temperatures and calculates the hydrolytic rates at these minimum pH values. *Id.* Kondritzer also calculates the half lives of atropine solutions for various pH values and temperatures. *Id.*

From measuring the rate of acid hydrolysis of atropine in aqueous solution, Kondritzer concludes that the predominant catalytic reaction above pH 4.5 involves the hydroxyl ion, and the predominant catalytic reaction below pH 3 involves the hydrogen ion. Ex. 1005, 4. Kondritzer also states:

The half lives of solutions of atropine at various pH values and temperatures can be calculated for both hydroxyl-ion and hydrogen-ion catalysis. The former accounts for the instability above approximately pH 5 and the latter for instability below approximately pH 3. The half life at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical.

Id.

Kondritzer states that “[a]s expected, the hydrogen ion catalyzed hydrolysis of atropine is slow.” Ex. 1005, 4. Based on the study, Kondritzer concludes that “[t]he pH for maximum stability of atropine in sterile aqueous solution varies between 4.11 at 0° and 3.24 at 100°.” *Id.* at 5.

4. *Analysis*

For its assertion that claims 1, 2, 4–9, and 12–19 would have been obvious over the combined teachings of Chia, Akorn, and Kondritzer, Petitioner relies on Akorn as teaching or suggesting adding to an atropine sulfate ophthalmic liquid composition a buffering agent to “provide a pH of from about 4.8 to about 6.4,” as required by claim 1. Pet. 28–31. Patent Owner challenges Petitioner’s reliance on Akorn asserting that the Petition fails to prove that Akorn was publicly available prior to the undisputed critical date of April 23, 2015, which Patent Owner also raised in its Preliminary Response. *See* PO Resp. 58–61; Prelim. Resp. 29–32. Patent Owner also challenges the testimony of Dr. Byrn in its Motion to Exclude Evidence asserting that “Dr. Byrn’s proffered opinions exceed his expertise, are not based on ‘scientific knowledge,’ ‘sufficient facts or data,’ and are not ‘the product of reliable principles’ and methods ‘reliably applied’ to the facts of this case.” Paper 29, 2 (“Mot. to Exclude”).

Because the prior art status of Akorn and Dr. Byrn’s testimony is relevant to all grounds asserted by Petitioner, we begin our discussion with these issues.

a) Prior Art Status of Akorn (Ex. 1004)

Petitioner has the burden to prove Akorn qualifies as prior art. *See In re Magnum Oil Tools*, 829 F.3d at 1376. “[A]t the institution stage, the petition must identify, with particularity, evidence sufficient to establish a

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reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication.” *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 (“*Hulu*”) at 13 (PTAB Dec. 20, 2019) (precedential).

“[P]ublic accessibility” is considered to be “the touchstone in determining whether a reference constitutes a ‘printed publication’ bar under 35 U.S.C. §102(b).” *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). “A given reference is ‘publicly accessible’ upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.” *SRI Int’l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

A determination whether a particular reference qualifies as a printed publication “is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis.” *Hall*, 781 F.2d at 899. In a proceeding before the Board, there is no presumption in favor of finding that a reference is a printed publication. *Hulu*, Paper 29 at 16.

During the institution phase of this proceeding, we authorized further briefing on the issue of whether Akorn was publicly accessible before the critical date, and each party filed a brief addressing this issue. *See* Ex. 3001; Paper 7; Paper 8. In our Institution Decision, we addressed the parties’ arguments and determined on the record before us at that time that “Petitioner has adequately shown for institution that Akorn was sufficiently accessible to the public interested in the art and searchable on the DailyMed website such that a POSA could have found it with reasonable diligence.”

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Dec. 27. In making this determination, we examined Petitioner’s additional evidence, Exhibit 1057, that it submitted with its reply to the preliminary response, and determined “that Petitioner properly relies on Exhibit 1057 as additional evidence to confirm that Exhibit 1004 was published and publicly accessible in July of 2014.” *See* Dec. 26–27.

In making this determination, we made the following findings concerning Exhibit 1057 for purposes of institution.

In particular, on the current record, we find that Petitioner’s Exhibit 1057 provides persuasive corroboration for its contention that Akorn was publicly accessible in July of 2014. Exhibit 1057 includes printouts of webpages from “DailyMed.” Ex. 1057. In the “ABOUT DAILYMED” section on the first page of the exhibit, there is a statement explaining that “The National Library of Medicine (NLM)’s DailyMed searchable database provides the most recent labeling submitted to the Food and Drug Administration (FDA) by companies and currently in use (i.e., ‘in use’ labeling).” *Id.* at 1. Among other items, the DailyMed “contains labeling for prescription and nonprescription drugs for human and animal use.” *Id.* The statement also explains that “[t]he NLM provides DailyMed to the public” and “[t]he labeling on DailyMed is typically reformatted to make them easier to read.” *Id.*

On the third page of Exhibit 1057, there is a copy of the DailyMed “LABELING ARCHIVES” webpage which depicts a “Labeling Archives Search,” with a first field for entering a drug name, and a second field for entering a date. *Id.* at 3. The webpage explains that “[t]his archive allows the user to retrieve the label current for a given date.” *Id.* Search results for the term “ATROPINE SULFATE” on “07/31/2014” are displayed. *Id.* There is an indication that the search provided 135 results which are listed in a row, apparently over a number of webpages. *Id.* The results are organized with the “DATE POSTED” identified in one column, along with the term “download” which appears to be formatted as a web link, and the “DRUG NAME” identified in a second column, wherein the drug name listed appears to be formatted as a web link. *Id.* Below the drug name, the name of

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the “Packager” is identified, along with a “Version” number. *Id.* Petitioner draws our attention to the label identified with July 24, 2014, as the “DATE POSTED,” “Atropine (atropine sulfate) solution/drops,” as the “DRUG NAME,” Akorn, Inc. as the “Packager,” with the “Version” noted as “7.” *Id.*

We understand the next page of the exhibit to be a copy of the DailyMed webpage depicting the version 7 label for Akorn’s atropine sulfate that was posted on July 24, 2014. Ex. 1057, 4. Based on our review, but for minor web-related formatting differences, this label posted on DailyMed appears to be the same as the label depicted in Exhibit 1004. In particular, we observe that both labels: (a) refer to “HIGHLIGHTS OF PRESCRIBING INFORMATION” for “Atropine Sulfate Ophthalmic Solution, USP 1% for topical application to the eye;” (b) include the “Revised: 7/2014” statement; (c) include the same indications and usage, dosage and administration; (d) set forth the same sections/subsections; and (e) describe the contents of the drug in the same manner, including the statement identifying inactives as: “benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.” *Compare* Ex. 1004, 1–5, *with* Ex. 1057, 4–6.

Taken together, we find that the evidence relied on in the Petition, i.e., Exhibits 1004, 1020, 1021, along with Exhibits 1056, 1058, and especially, 1057, submitted with the Reply, provide strong indicia that the July 2014 version of Akorn’s atropine sulfate drug label represented on the current record as Exhibit 1004 was posted on July 24, 2014, on the DailyMed website. We do not find any dispute on the current record that DailyMed is a federal government website that is accessible to the public and presented in a manner that allows the public to readily search its database for drug labels that have been approved by the FDA. Moreover, as Petitioner asserts, the DailyMed website explains, “The DailyMed RSS feed provides updates and information about new drug labels approved by the FDA and published on NLM’s DailyMed Web site.” Ex. 1057, 1. In other words, the DailyMed website further extends its reach to the public through such feed.

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Dec. 23–25.

Patent Owner in its Response continues to question the public availability of Akorn. *See* PO Resp. 58–60. Patent Owner continues to assail the public availability of Akorn as shown by the exhibits originally presented with the Petition, *see id.*, but we agreed with some of these criticisms. For instance, we stated:

To begin, we note that, in some respects, we agree with Patent Owner’s position. For example, we agree with Patent Owner that the “7/14” revision date printed on Akorn, on its own, indicates only that some unknown author(s) modified the document on that date. *See* Prelim. Resp.30, PO Sur-reply 2–3. Indeed, similar to the copyright or creation dates in *Hulu*, the revision date, by itself, is insufficient to demonstrate that the exhibit was publicly available on that date. *See Hulu*, Paper 29 at 19. We also agree with Patent Owner that neither the FDA approval date of the Akorn atropine sulfate drug product nor the sale or use of that product demonstrates the public accessibility of drug label reflected in Akorn prior to the critical date. *See* Prelim. Resp. 30, PO Sur-reply 2–3.

Dec. 23. Our decision on the public availability of Akorn turned on the additional evidence Petitioner submitted as Exhibit 1057. *See id.* at 23–27.

The only criticism Patent Owner presents with reference to our analysis of Exhibit 1057 as set forth above is to question a statement on the DailyMed webpage concerning when filtering by published date was added to Web Services. *See* PO Resp. 60; Sur-Reply 25. Patent Owner states: “But Petitioner’s DailyMed exhibit (created on September 15, 2021) acknowledges that “Filtering by Published Date [Was] Added to Web Services” only as late as October 2015 (EX1057, 1, 2), which falls after the critical date. EX1001, Cover. As the very same search means that Petitioner used to find the label in EX1057 admittedly did not exist before

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the critical date, Petitioner has failed to demonstrate pre-critical date public availability of this new label.” PO Resp. 60.

We find that Patent Owner’s criticism misses the mark. Petitioner is using the DailyMed exhibit as further evidence that Akorn was publicly available as of the revision date of 7/2014 as shown on Akorn, Ex. 1004. *See* Reply 1 (“As set forth in the Petition, EX1004, a drug label to Akorn, bears July 2014 revision dates that comport with its FDA approval and publication well before the critical date. *See* Pet., 9; *Hulu*, 13. It also bears Akorn’s corporate insignia. EX1004, 5. Additional evidence confirms these dates are reliable. EX1056-58.”); 3 (“Public records from DailyMed, part of the NIH’s National Library of Medicine, show that EX1004 was posted publicly on **July 24, 2014**.”). Whether a POSA could have searched this way for labels published before the critical date is irrelevant; Petitioner is only using the evidence to show that Akorn was, in fact, published in July 2014, before the critical date on a searchable website. *See id.* Patent Owner does not dispute that DailyMed was searchable by drug name, which would be the logical way a POSA would search such a database for information for a drug of interest.

Petitioner also provides further evidence that the Akorn label was published on July 24, 2014, through a response by the National Library of Medicine (“NLM”) to a Freedom of Information Act request. *See* Ex. 1071. In this Freedom of Information Act request, Petitioner asked for written confirmation that the substance of the Akorn label was posted on July 24, 2014 on the DailyMed website. *Id.* The National Institutes of Health (“NIH”) responded that version 7 of the Akorn label was published on DailyMed on July 24, 2014, and provided the URL that is reflected in the Akorn label in Exhibit 1057 from the DailyMed website. *See* Ex. 1072, 6;

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Ex. 1057, 4–7. NIH also confirmed that NLM “received version 7 of this label from the FDA on 07/24/2014 @ 2:15:04 PM,” “published version 7 on DailyMed on the same day, 07/24/2014 @ 14:59:48 PM,” and confirmed that “NLM does not make changes to the content contained within any SPL [or structured product labeling] records that it receives from the FDA.”

Ex. 1072, 6. We find that Petitioner has provided more than sufficient evidence that the Akorn label reflected in Ex. 1004 was publicly available before the critical date.

For the reasons set forth above, we determine that Petitioner has shown by a preponderance of the evidence that Akorn, Ex. 1004, is a printed publication that was publicly available before the critical date.

b) Patent Owner’s Motion to Exclude Evidence

Patent Owner moves to exclude from evidence the Declaration of Dr. Byrn (Ex. 1002), Exhibits 1004 and 1057 that constitute the Akorn labels, and Exhibits 1079 through 1088 that Petitioner submitted with its Reply. Mot. to Exclude 2. Petitioner filed an Opposition (Paper 30, “Opp. to Mot. to Exclude”), and Patent Owner filed a Reply (Paper 32, “Reply to Mot. to Exclude”). For the following reasons, Patent Owner’s Motion to Exclude is *denied*.

Pursuant to our Rules, a motion to exclude evidence must be filed to preserve any previously-made objections to evidence. 37 C.F.R. § 42.64(c). The motion must identify where in the record the objections were made, and must explain the objections. *Id.* Patent Owner appropriately identifies where in the record it previously served objections to the exhibits it seeks to exclude. Mot. 2 (citing Papers 12, 22).

As the moving party, Patent Owner bears the burden of proof to establish that it is entitled to the requested relief, i.e., the exclusion of evidence as inadmissible under the Federal Rules of Evidence (“FRE”). *See* 37 C.F.R. §§ 42.20(c), 42.64(a).

(1) Dr. Byrn’s Testimony (Ex. 1002)

Patent Owner challenges Dr. Byrn’s testimony under FRE 702 as not based on sufficient “scientific knowledge,” not based on “sufficient facts or data,” and not “the product of reliable principles” and methods “reliably applied” to the facts of this proceeding. Mot. to Exclude 2.

(a) Requisite Scientific Knowledge

For instance, although Dr. Byrn agrees that the ’787 patent is “directed to the field of ophthalmic compositions and ophthalmic solutions,” Patent Owner asserts that Dr. Byrn’s curriculum vitae (Ex. 1002, Appendix A) “provides no indication that Dr. Byrn has any expertise in ophthalmic formulation.” Mot. to Exclude 2–3 (citing Ex. 2009, 97:19–98:14, 104:20–106:5). Patent Owner further states:

During his deposition, Dr. Byrn identified brief eyedrop forays (none significant enough to merit mention in his CV or declaration), but could not identify any ophthalmic product he formulated before the critical date. Even as of 2021, Dr. Byrn never had primary responsibility for formulating any drug product that has received regulatory approval or been commercialized.

Mot. to Exclude 3 (citing Ex. 2010 ¶ 8). Patent Owner also criticized Dr. Byrn’s alleged lack of knowledge of ophthalmic terms such as lacrimation. *See id.*

Petitioner responds that the primary focus in evaluating the admissibility of testimony under FRE 702 is “whether an expert’s opinion

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will assist the trier of fact,” a low bar, and many of Patent Owner’s criticisms go to the weight to be accorded Dr. Byrn’s testimony rather than its admissibility. Opp. to Mot. to Exclude 1–6. In applying FRE 702, Petitioner asserts that “Dr. Byrn, a professor of medicinal chemistry who specializes in drug formulation, is eminently qualified to opine about the straightforward formulation issues presented in this proceeding.” *Id.* at 1.

Petitioner asserts that Patent Owner does not contest that Dr. Byrn meets Petitioner’s POSA definition (as we have determined should be applied in this proceeding), but even if we required experience in formulating ophthalmic pharmaceuticals, we find that Dr. Byrn has such experience. *See* Opp. to Mot. to Exclude 2–4; Ex. 1002, Appendix A ¶¶ 3–10. Petitioner asserts that Dr. Byrn testifies that:

[H]e worked as a consultant for Alcon—a well-known eye care company—on a number of ophthalmic products, including ones that were FDA-approved, prior to the critical date. *See* Ex. 2009, 136:12–137:12. He further testified that he worked with eye drops as part of Purdue’s Africa program. *Id.* at 49:149–50:2.

Id. at 4. Petitioner also asserts that Dr. Byrn accurately described the term “lacrimation” in his deposition. *Id.* at 4 n.2 (citing Ex. 2009, 49:11–14; Ex. 1002 ¶ 77 (quoting Ex. 1047, 2)).

As we have previously determined, a POSA need not have specific experience in ophthalmic formulation. *See* Section II.B. Dr. Byrn has ample experience to qualify as a POSA, which we defined as a person having a Ph.D. in chemistry, organic chemistry, physical chemistry, or pharmaceuticals, with several years of experience preparing and/or testing pharmaceutical formulations at the time of the purported invention. *Id.*; *see* Ex. 1002 ¶¶ 3–10. Dr. Byrn has the requisite academic background, as well as extensive experience in drug development and formulation. *See* Ex. 1002

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¶¶ 3–10. Dr. Byrn testifies that his “laboratory has done extensive research on drug formulations, and [he has] authored over two hundred book chapters and peer-reviewed journal articles on properties of a wide variety of pharmaceutical compositions.” *Id.* ¶ 10.

We also find, however, that Dr. Byrn has experience with ophthalmic formulations. Dr. Byrn testifies that he has “worked quite a bit with eyedrops” in Purdue’s Africa program. Ex. 2009, 49:21–24. In his Declaration, Dr. Byrn testifies that he was a co-founder of the Sustainable Medicines in Africa in the Kilimanjaro and Arusha regions of Tanzania in 2007. Ex. 1002 ¶ 5. Dr. Byrn describes this program more extensively in his curriculum vitae as providing educational programs that are “aimed at providing source of well-trained manufacturing scientists for pharmaceutical industry in Tanzania and Africa,” and including a GMP-level pharmaceutical manufacturing facility to teach manufacturing under strict quality control, as well as a quality medicines laboratory equipped with HPLCs. Ex. 1002, Appendix, 101. Dr. Byrn also testifies that he consulted with Alcon on a number of ophthalmic drug products although he was not primarily responsible for their formulation. *See* Ex. 2009, 136:12–20.

We find Dr. Byrn’s alleged lack of “primary” responsibility for the formulation of an ophthalmic product to be somewhat of a red herring in assessing whether Dr. Byrn has “expertise in ophthalmic formulation” as Patent Owner asserts should be required. *See* Mot. to Exclude 2–3. In response to questions about whether Dr. Byrn ever had primary responsibility for formulating a drug product that has received regulatory approval, Dr. Byrn testifies that he has “been on a team that formulated drug products for both for commercial sale and IND testing.” Ex. 2009, 134:19–24. Dr. Byrn also pointed out what he considered to be a false premise in

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the questions related to “primary” responsibility for drug formulation.

Dr. Byrn testifies:

I have been a consultant on a large number of products that came on the market and I worked in a team, and my work was – part of the work was critical for certain specifications and certain marketing steps, but I don’t believe that in this day and age a person is primarily responsible for bringing a drug on the market; it’s a team activity.

Id. at 135:15–23. We credit Dr. Byrn’s testimony here.¹² We also determine that Dr. Byrn satisfies the requirements for a POSA as we have determined it should be defined, without specific expertise in ophthalmic formulation, but also determine that even if we applied Patent Owner’s heightened standard requiring such expertise, Dr. Byrn satisfies that definition also. Dr. Byrn has the requisite scientific knowledge to serve as an expert for Petitioner.

(b) Sufficiency of Underlying Facts and Data; Reliability of Principles and Methods as Applied to Underlying Facts and Data

Patent Owner asserts that Dr. Byrn’s alleged inexperience with ophthalmic formulations led him to offer an opinion not based on sufficient facts or data or reliable principles, i.e., that Dr. Byrn’s opinion that “Akorn teaches the uses of buffering agents to achieve a solution pH range of 3.5 to 6.0 were ‘premised’ on an undisclosed assumption that the buffering range of the weak acid extends ± 2 pH units away from its pK_a .” Mot. to Exclude 4

¹² We also find that Dr. Byrn was clearly familiar with the term “lacrimation,” which means “the secretion of tears especially when abnormal or excessive,” but chose to use the word “tearing” instead. See Ex. 2009, 49:3–14; see also <https://www.merriam-webster.com/dictionary/lacrimation> (accessed June 25, 2023) (defining lacrimation).

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(citing PO Resp. 39–40; Ex. 2009, 96:5–97:4; Ex. 1002 ¶¶ 20, 24, 65–66, 80, 87, 94–95, 99, 154–55, 158, 167, 171, 200, 201, 208, 214, 220). Patent Owner also asserts Dr. Byrn’s assumption has been shown to be incorrect in a district court proceeding in which he testified. *See* Mot. to Exclude 4–7.

Petitioner counters that Dr. Byrn’s opinions are based on sufficient facts and data and are reliable. *Opp. to Mot. to Exclude* 5–6. As an example, Petitioner points to Dr. Byrn’s reliance on Remington (Ex. 1019), which Dr. Laskar admits is a formulator’s “bible,” to establish that “Remington means exactly what it says: buffer capacity represents a compromise between stability and comfort, and thus a buffer with diminished capacity (*e.g.*, the one provided by sodium phosphate salts) should be used.” *Opp. to Mot. to Exclude* 5 (citing Ex. 2003 ¶¶ 62–63; Ex. 1002 ¶¶ 97–98).

Petitioner also points to support for Dr. Byrn’s opinion that sodium phosphate salts “can still buffer outside of ± 1 unit away from their pK_a ” in the “reliable scientific literature that Patent Owner seeks to preclude the Board from considering.” *Opp. to Mot. to Exclude* 6 (citing Exs. 1079–1083 (buffer recipes using the claimed sodium phosphate salts below pH 6.0)). Finally, Petitioner asserts that Dr. Byrn’s testimony in the district court proceeding is inapposite because

The primary legal issue in that case dealt with infringement under the doctrine of equivalents, and whether a generic company’s “proposed product contains an equivalent to the ‘buffer’ of the claims[.]” *See* Ex. 2010, 2. Unlike here, the alternative excipient that the generic company contended was a buffer had not be identified, disclosed, and claimed as such by the patentee. *See* Ex. 1001 (claim 7).

Id. at 6–7.

We agree with Petitioner here that Patent Owner's concerns about the sufficiency of the support for Dr. Byrn's opinions goes more to the weight to be accorded such opinions rather than a need to exclude such opinions. *See* TPG 40–41, 79 (“A motion to exclude must explain why the evidence is not admissible (e.g., relevance or hearsay) but may not be used to challenge the sufficiency of the evidence to prove a particular fact.”). We also note that the findings in the district court litigation are based on a different record that is not before us here. For instance, the district court relies on a Lewis reference and a Harris reference that is not before us and testimony from Dr. Richard Moreton that is also not before us here. *See* Ex. 2010 ¶¶ 63–69. Therefore, we determine that the district court's findings are not sufficiently probative of the questions before us here.

Also, the district court's findings are not as definitive as Patent Owner states. The patent owner in the district court case attempted to prove infringement by the doctrine of equivalents for a formulation that did not expressly contain a buffer, but that it argued inherently contained a buffer from the chemical disassociation of the active ingredient in the product. *See* Ex. 2010, 64–65. The district court found that patent owner failed to prove that this actually occurs in the accused product. *Id.* at 65. The district court case is in stark contrast with the underlying facts of this proceeding in which the prior art formulation expressly contains the same buffers as claimed in the '787 patent. *See* Ex. 1001, 98:7–10 (claim 7); Ex. 1004, 3.

(c) Conclusion

Based on the foregoing, we *deny* Patent Owner's motion to exclude Exhibit 1002, Dr. Byrn's testimony.

(2) The Akorn Labels (Exs. 1004 and 1057)

Patent Owner asserts that Exhibits 1004 and 1057 should be excluded because Petitioner failed to show that Exhibit 1004 (Akorn) was publicly available before the critical date, and Exhibit 1057 is deficient to show such public availability of Exhibit 1004. Mot. to Exclude 7–8.

We have previously addressed these issues in our determination of the prior art status of Akorn, Ex. 1004, set forth above. *See* Section II.D.4.a). For these same reasons, we *deny* Patent Owner’s motion to exclude Exhibits 1004 and 1057.

(3) Exhibits 1079–1088

Patent Owner moves to exclude Exhibits 1079 through 1088 submitted with Petitioner’s Reply. *See* Mot. to Exclude 2, 8–15. Patent Owner asserts that these exhibits should have been submitted with the Petition and are untimely. *Id.* at 8. Patent Owner also asserts that Dr. Byrn did not “elect to submit a Reply declaration, rely upon any of these documents, or testify that any of them are the kinds of documents an expert in his field (much less a POSA in the field of the invention) would rely upon.” *Id.*

Petitioner asserts that these documents were presented to Dr. Laskar at his deposition to rebut Patent Owner’s assertions that “two common buffering agents, sodium dihydrogen phosphate and disodium hydrogen phosphate—identified and claimed by the ’787 patent as buffering agents—are not buffers in the claimed range of about 4.8 to about 6.4.” Opp. to Mot. to Exclude 10–11 (citing PO Resp. 35–36; Ex. 2003 ¶ 56).

Our Trial Practice Guide states that:

Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima

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facie case of unpatentability. A party may also submit rebuttal evidence in support of its reply.

Patent Trial and Appeal Board Consolidated Trial Practice Guide 73 (Nov. 2019) (citing *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1077–78 (Fed. Cir. 2015)).

Here, we find that Exhibits 1079 through 1088 are appropriate rebuttal evidence. Petitioner uses these exhibits to test Dr. Laskar’s opinions concerning the buffering range for sodium dihydrogen phosphate and disodium hydrogen phosphate. *See generally* Ex. 1078, 91–189.¹³ As the Federal Circuit noted in *Belden*, there is no bright-line demarcation between support for Petitioner’s prima facie case and rebuttal evidence. For instance, the Federal Circuit stated that using rebuttal evidence as support for the prima facie case does not necessarily mean that it was “necessary” for the prima facie case requiring it to be in the Petition.

Evidence admitted in rebuttal to respond to the patent owner’s criticisms will commonly confirm the prima facie case. That does not make it necessary to the prima facie case. And nothing required the Board to write its opinion to separate the material offered by [petitioner] at different stages of the proceeding.

See Belden, 805 F.3d at 1079.

For these reasons, we *deny* Patent Owner’s motion to exclude Exhibits 1079 through 1088.

¹³ In response to Patent Owner’s Objections to Evidence, Petitioner also provided a Declaration of Rebecca L. Baker, a Research Analyst at the law firm representing Petitioner, attesting to the authenticity of Exhibits 1079, 1081–1085. *See* Ex. 1095.

c) Claim 1

Petitioner asserts that claim 1 recites elements previously known in Chia and Akorn: “Chia’s low-concentration atropine formulation, combined with Akorn’s buffering agents to provide an aqueous atropine solution with a pH range that was well known to be desirable for treating myopia.” Pet. 23. The claimed “stabilized” atropine solution of claim 1, Petitioner asserts, is an expected result of the combination of Chia’s low-concentration atropine formulation and Akorn’s buffering agents. *Id.*

Petitioner describes what it terms the “ample” motivation to make such a combination and the reasonable expectation of success for such a combination as follows. *See* Pet. 23 (citing Ex. 1002 ¶¶ 64–78).

In 2012, *Chia* disclosed that low-concentration atropine eye drops effectively treated myopia and reduced patient compliance problems associated with higher concentration compositions. Ex. 1003, 7–8. *Chia*’s clinical success would have provided motivation to make and use low-concentration atropine formulations at optimal pH levels for patient comfort and stability. To determine the suitable pH levels, a POSA would have looked to FDA-approved atropine ophthalmic solutions. Ex. 1002 ¶¶ 65, 87. As a result, a POSA would have been motivated to use *Akorn*’s pH range of 3.5–6.0 for the low-concentration formulation disclosed in *Chia*. A POSA would have confirmed that this range was appropriate via routine experimentation and based on the predicted stability of atropine at various pHs disclosed in *Kondritzer*.

Pet. 23–24.

Patent Owner responds that Akorn “does not disclose the phosphate salts are buffering agents. Nor does it disclose that the Akorn product has a pH range of 3.5–6.0. Each of these failures is case-dispositive,” as all grounds rely exclusively on Akorn “to disclose a stabilized atropine ophthalmic aqueous solution comprising a buffering agent to provide a pH

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within the claimed range.” PO Resp. 1, 26. Patent Owner also asserts that Petitioner’s only motivation for making the claimed combinations in the ’787 patent results from improper hindsight. *See id.* at 43–52.

(1) Limitations 1[a], 1[b], 1[d], and 1[e]

We begin our analysis with the limitations of claim 1 that Patent Owner does not dispute are taught by the prior art. Petitioner points to both Chia and Akorn as teaching limitation 1[a]: “[a] stabilized ophthalmic composition for treating pre-myopia, myopia or progression of myopia.” Pet. 28–29; *see* Ex. 1002 ¶¶ 83–87. Chia describes the ATOM2 study, which “examined the effect of lower doses of atropine to determine whether these concentrations could result in efficacy in preventing myopia progression, with less visual side effects (i.e., pupil dilation, loss of accommodation, and near vision blur).” Ex. 1003, 1–2. The treatment phase of the ATOM2 study lasted 24 months, *id.* at 2, and “[t]rial medications were prepackaged so that bottles were prelabeled with subject number and of similar appearance. Trial medication consisted of the appropriate dose of atropine sulfate with 0.02% of 50% benzalkonium chloride as a preservative” *Id.*

From this description, Dr. Byrn testifies that “the atropine eye drops discussed by *Chia* teach ‘an ophthalmic composition.’” Ex. 1002 ¶ 85. Dr. Byrn further testifies that “a POSA would have recognized that *Chia*’s ‘prepackaged’ composition, administered over the course of a multi-year study, would almost certainly have included components to reduce degradation of atropine—i.e., a POSA would have recognized that the formulation in *Chia* was stabilized.” *Id.* ¶ 86 (citing Ex. 1003, 2). We agree

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with Dr. Byrn’s assessment of the teachings of Chia and credit his testimony.¹⁴

Petitioner relies on Chia for teaching limitation 1[b]: “from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water.” Pet. 29–30. Petitioner relies on the statement in Chia that “[a]tropine 0.01 % has minimal side effects compared with atropine at 0.1 % and 0.5%, and retains comparable efficacy in controlling myopia progression,” as teaching an aqueous 0.01 % atropine solution that “falls squarely within the claimed range of limitation 1[b]. *Id.* at 29–30; Ex. 1002 ¶ 89.

We agree with Petitioner that the overlap between the concentration of Chia’s atropine solution and the claimed range establishes a *prima facie* case of obviousness, for which Patent Owner has not offered any rebuttal. *See Genentech, Inc. v. Hospira Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020) (citing *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)).

Concerning limitation 1[d]: “the stabilized ophthalmic composition is a liquid,” we agree that both Chia and Akorn teach aqueous, i.e., liquid solutions. *See* Pet. 32–33 (citing Ex. 1002 ¶¶ 101–103; Ex. 1004, 1–5; Ex. 1003, 1). As Petitioner states, “[b]oth *Chia* and *Akorn* disclose topical administration of atropine solutions by instillation of eyedrops, and a POSA

¹⁴ Dr. Byrn also relies on Akorn’s disclosure of “an FDA-approved, commercially available atropine sulfate ophthalmic solution,” as also teaching a stabilized ophthalmic composition for treating myopia. Ex. 1002 ¶ 87. Dr. Byrn testifies that “[a] POSA would have understood that *Akorn* discloses a stabilized ophthalmic composition via its disclosure of several buffering agents to adjust pH to a range of 3.5–6.0, including monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide.” *Id.* Because whether Akorn discloses buffers or a pH range of 3.5–6.0 for its solution is disputed by Patent Owner, we will address Akorn’s teachings when we address Patent Owner’s criticisms of Petitioner’s case below.

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would have understood that each solution would be a liquid.” Pet. 33 (citing Ex. 1002 ¶¶ 102–103; Ex. 1019, 49). We agree with Dr. Byrn that a POSA would have understood that the ophthalmic composition in Chia and Akorn were liquids.

Limitation 1[e] requires that “the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.” Ex. 1001, 97:38–44.

Petitioner asserts that limitation 1[e] is “merely an obvious, known, and/or inherent property of the obvious formulation claims in elements 1[a]–[d].” Pet. 34. Petitioner further states that the percentage of “a degradant,” such as tropic acid from the breakdown of atropine in an aqueous solution, “is simply a property inherent to the atropine or atropine sulfate ophthalmic solution.” Pet. 33 (citing Ex. 1002 ¶¶ 43, 105). Petitioner relies on the teachings of Kondritzer to show that limitation 1[d] is an inherent property of the composition, i.e., that the limit on the amount of degradation products under the claimed conditions necessarily results from the claimed stabilized ophthalmic composition. *See* Pet. 34; *see In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (determining claim limitation directed to an inherent property of a formulation “adds nothing of patentable consequence”).

For instance, Dr. Byrn testifies that “*Kondritzer* shows that atropine degradation was a predictable function of pH and temperature. Ex. 1005, 1, 4–5. *Kondritzer* derives an equation to predict the pH at which atropine would be most stable for any hydrogen ion concentration. Ex. 1005, 2.” Ex. 1002 ¶ 106. Dr. Byrn also testifies that Kondritzer shows in Figure 10 that “at 20° C and pH 5, the half-life of atropine is 266 years; and at 20° C

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and pH 6, the half-life of atropine is 27 years.” Ex. 1002 ¶ 107. Dr. Byrn utilized Kondritzer’s chart in Figure 10 to calculate the time it would take for 10% of atropine to degrade at a pH of 5 and 20° C. *Id.* Dr. Byrn concludes that “at 20° C and pH 5, a POSA would reasonably expect the compositions of claim 1 to comprise 90% atropine for approximately 40.4 years. At these parameters, which fall within the limitations of claim 1, *Kondritzer* shows that atropine would readily exceed the stability requirements of limitation 1[e], which allows for up to 10% degradation after at least two weeks.” *Id.* ¶ 108.

We credit Dr. Byrn’s testimony concerning the teachings of Kondritzer and the ability of a POSA to predict the amount of degradation of atropine over time.¹⁵ Therefore, we find that Petitioner has shown that limitation 1[e] is inherent in the stabilized ophthalmic solution of claim 1.

(2) Limitation 1[c]

The heart of the parties’ dispute in this case involves whether the cited art teaches limitation 1[c] that requires “the stabilized ophthalmic

¹⁵ Dr. Laskar faults Dr. Byrn’s statement that the humidity of the ambient air “would not be expected to affect the stability of atropine molecules that are in solution.” Ex. 2003 ¶ 131; *see* PO Resp. 55–56. Dr. Laskar states that “Dr. Byrn should be aware that the relative humidity of the ambient air can impact the rate of evaporation of the water in the atropine solution, which could then impact the concentration of atropine,” especially when stored in a plastic dropper bottle that is semi-permeable to water. Ex. 2003 ¶ 131. Dr. Byrn’s testimony, which we credit, finds that the expected degradation of an atropine solution of claim 1 would not only retain 90% atropine for the required two weeks, but for 40.4 years. It is hard to imagine in what scenario the relative humidity could so diminish the stability of an atropine solution made in accordance with claim 1 that it would fail to meet the 2-week limitation to preserve at least 90% of the atropine.

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composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4.” *See* Pet. 30–32; PO Resp. 26–43.

Petitioner relies on Akorn, asserting it discloses “a stabilized ophthalmic composition” that further discloses “several buffering agents to ‘provide a pH of from about 4.8 to 6.4,’ as in claim 1.” Pet. 30–31.

Petitioner further asserts that:

Kondritzer would have provided a reasonable expectation of success to use *Akorn*’s pH range of 3.5–6.0. Ex. 1002 ¶¶ 96–99. *Kondritzer* discloses that optimum atropine stability in aqueous solutions is at pH 3 to 5, and predicts atropine stability in the pH range of 2 to 7. Ex. 1005, 4; Ex. 1002 ¶ 96. However, overly acidic pH was known to be a problem for patient comfort in ophthalmic solutions. Ex. 1002 ¶ 97. A POSA would therefore have targeted the higher end of *Akorn*’s stability range and been motivated to use a pH range of about 5 to about 6 to optimized stability in view of patient comfort. Ex. 1002 ¶¶ 98–99; Ex. 1019, 52 (ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4); *see also* Ex. 1005, 4 (showing decreasing atropine stability as pH increases to 7.0). Thus, a POSA would have recognized that a pH range of approximately 3.5–6.0 was optimal. Ex. 1002 ¶ 99.

Id. 31. Petitioner concludes that “[b]ecause pH was a well-known result-effective variable, and because these ranges significantly overlap with the claimed pH range of 4.8 to about 6.4, the claimed range would have been obvious.” *Id.* at 32 (citations omitted).

Patent Owner disagrees. Patent Owner asserts that “all grounds critically hinge on using the same ‘buffer system’ and pH range allegedly disclosed in [Akorn].” PO Resp. 30. But, Patent Owner asserts that Akorn does not state that it employs a buffering agent to control or maintain pH of its atropine solution, and does not even disclose the actual pH of its solution. *Id.* at 26. Patent Owner also asserts that the phosphate salts disclosed in

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Akorn are not identified as buffering agents, and could not have buffered Akorn's solution at the listed pH range. *Id.* at 27. Dr. Laskar testifies that in listing the pH range of 3.5 to 6.0, Akorn is merely showing compliance with the pH limits imposed by the National Formulary of the U.S. Pharmacopeia ("USP") and does not state the pH of the described solution. PO Resp. 1, 33–35. Patent Owner also asserts that there is no indication in Akorn that the listed phosphate salts act as buffers, so these could not have "provided" the pH range as required by the claims. *Id.* at 34–35.

Akorn describes the ingredients of its formulation as follows.

Each mL of Atropine Sulfate Ophthalmic Solution USP, 1% contains: **Active:** atropine sulfate 10 mg equivalent to 8.3 mg of atropine. **Inactives:** benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium Hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.

Ex. 1004, 3.

Patent Owner's argument rests on a listed buffering range in the Waterman reference for phosphoric acid that does not encompass a pH of 3.5 to 6.0 as set forth in Akorn. *See* Ex. 2003 ¶ 52; Ex. 1040, 23. As Dr. Laskar testifies, "Waterman Table 8 lists the 'Buffering Range' of Phosphoric acid as '2–3.1, 6.2–8.2.'" Ex. 2003 ¶ 52 (citing Ex. 1040, Table 8). Dr. Laskar testifies:

As the Waterman reference submitted with the petition explains, when selecting a buffer, which acts to maintain a solution pH (e.g., at the pH of maximum stability of the active ingredient), the "primary criteria for selection" are "the pH range and buffer capacity [which is maximal at a pH value equal to the pK_a of the buffer (164)] for the buffer." Ex. 1040, 23 (bracketed in material in original). Waterman states that its "Table 8 lists commonly used buffers along with their pK_a

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values and optimal pH ranges.” *Id.* Waterman Table 8 lists the “Buffering Range” of Phosphoric acid as “2–3.1, 6.2–8.2.” *Id.*, Table 8; *see also* paragraph 9 above. In other words, the buffering range of phosphoric acid and its dibasic sodium phosphate and monobasic sodium phosphate salts does not cover or even overlap with a solution pH of 3.5–6.0.

Ex. 2003 ¶ 52.

Patent Owner’s argument presumes that the pK_a for a particular buffer is set at a particular pH range which is not malleable depending on the conditions of the solution that is being buffered. Waterman itself refutes this presumption. First, Waterman describes the buffering ranges listed in Table 8 as “optimal” pH ranges of $pK_a \pm 1$ indicating some buffering capacity may exist below or above the given ranges. *See* Ex. 1040, 23. Dr. Byrn testifies that the most effective pH range for a buffer is within ± 1 of its pK_a , but “[i]t’s not a hard cutoff; it’s an effectiveness issue.” Ex. 2009, 87:5–12; *see id.* at 88:23–89:19 ($pK_a \pm 1$ covers the most effective buffer range, but it is not a hard cutoff), 91:7–18 (person of skill knows $pK_a \pm 1$ is not a hard cutoff); 95:11–97:4 (applying the Henderson, Hasselbach equation provides a wider pH buffering range than $pK_a \pm 1$). Dr. Laskar testifies that pK_a changes as a function of temperature. Ex. 1078, 124:5–9. Waterman also states that “[u]se of co-solvents, surfactants, and complexing agents to solubilize a drug may also influence that buffering capacity and final pH of a formulation by altering the effective pK_a of the buffer and/or directly interacting with the buffer components.” Ex. 1040, 24. The evidence of record indicates that the pK_a for a buffer is not static, but depends on the parameters of the solution in which the buffer is used.

As for the specific phosphate buffers used in Akorn and claim 7 of the ’787 patent, Petitioner submitted credible evidence that the lower end of the

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buffer range for these buffers may be as low as pH 5.4. For instance, in Chapter 4 of the Fifth Edition of the European Pharmacopoeia, with which Dr. Laskar testifies he is familiar and which contains recipes for various buffer solutions, is described a 0.067 molar phosphate buffer solution with a pH of 5.4 that is within the 3.5 to 6.0 pH range set forth in Akorn. *See* Ex. 1081, 6; Ex. 1078, 113:12–118:20; *see also* Ex. 1078, 115:22–116:5 (stating European Pharmacopoeia provides a recipe for an 0.067 molar phosphate buffer solution pH 5.4 within the 3.5 to 6.0 pH range).

Petitioner also presents further evidence of a phosphate buffer with a pH range of 5.8 to 8.0 as set forth in a book titled “Buffers: A guide for the preparation and use of buffer in biological systems,” by Calbiochem, an affiliate of Merck KGaA. *See* Ex. 1082, 1, 2, 25. The excerpt showing the recipe is set forth in a screenshot, which is reproduced below. Ex. 1082, 25.

6. Phosphate Buffer; pH range 5.8 to 8.0

(a) 0.1 M Sodium phosphate monobasic; 13.8 g/l (monohydrate, M.W. 138.0)

(b) 0.1 M Sodium phosphate dibasic; 26.8 g/l (heptahydrate, M.W. 268.0)

Mix sodium phosphate monobasic and dibasic solution in the proportions indicated and adjust the final volume to 200 ml with deionized water. Adjust the final pH using a sensitive pH meter.

ml of Sodium phosphate, Monobasic	92.0	81.5	73.5	62.5	51.0	39.0	28.0	19.0	13.0	8.5	5.3
ml of Sodium phosphate, Dibasic	8.0	18.5	26.5	37.5	49.0	61.0	72.0	81.0	87.0	91.5	94.7
pH	5.8	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0

The screenshot above shows a recipe and accompanying table for making an aqueous phosphate buffer having a pH between 5.8 and 8.0 by mixing 0.1 M sodium phosphate monobasic with 0.1 M sodium phosphate dibasic in deionized water.

Petitioner further presents evidence from PubChem from the National Institutes of Health on the pK_a values for Monosodium phosphate and

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disodium hydrogen phosphate. *See* Exs. 1084, 1085. The first publication lists the pK_a for monosodium phosphate as a range from 6.8–7.2 “depending on the physiochemical characteristics during pK_a determination.” Ex. 1084, 7. The second publication lists the pK_a ’s for disodium hydrogen phosphate in the following table, which differ from those set forth in the Waterman reference. Ex. 1085, 8.

3.2.13 Dissociation Constants

$pK_{a1} = 2.15$; $pK_{a2} = 6.83$; $pK_{a3} = 12.38$ (phosphoric acid), all at 25 °C

Sigma-Aldrich; Sodium phosphate dibasic. S9763. Sigma-Aldrich, St. Louis, MO. Available from, as of Nov 30, 2006: <https://www.sigmaaldrich.com/catalog/search/ProductDetail/SIAL/S9763>

The table is table 3.2.13 from the PubChem listing for Disodium hydrogen phosphate, showing pK_a values for dissociation of 2.15, 6.83, and 12.38 at 25° C.

With this record evidence in mind, we turn to what a POSA would glean from reviewing Akorn. Dr. Byrn testifies that Akorn discloses standard buffering agents, including dibasic sodium phosphate, also known as disodium hydrogen phosphate, and monobasic sodium phosphate, also known as sodium dihydrogen phosphate, that have been shown in the evidence just discussed to be able to buffer Akorn’s formulation at least in the upper part of the cited pH range. Ex. 1002 ¶ 94–95 (citing Ex. 1019, 52; Ex. 1026, 4–5). We disagree with Dr. Laskar’s reliance solely on the Waterman reference as disclosing a buffering range for phosphate salts that “has no overlap with a solution pH of 3.5 to 6.0,” and do not credit his conclusion that a POSA would understand this lack of overlap “to completely contradict Dr. Byrn’s assertions that these phosphate salts represent a ‘common buffer’ that was used in EX1004 ‘to maintain a pH of 3.5 to 6.0.’” *See* Ex. 2003 ¶ 78.

We do not agree with Dr. Laskar's criticism that Akorn does not disclose buffers. *See* Ex. 2003 ¶¶ 71–72. Dr. Laskar testifies that Akorn does not disclose any buffers. *Id.* Dr. Laskar further testifies:

To the contrary, the disclosure of EX1004 is consistent with the direction provided in Remington and the state of the art in 2015 regarding atropine aqueous ophthalmic solutions. Everything I have read in EX1004 is consistent with the state of the art before 2015, which was to avoid using a buffer or buffering agent in the acidic solution of storage within the boundaries (pH 3.5–6.0) imposed by the USP.

Ex. 2003 ¶ 71.

We find, however, that Dr. Laskar's statements concerning the state of the art in 2015, including about the teachings of the Remington reference, are not sufficiently supported by record evidence. For instance, Dr. Laskar premises his conclusion concerning the state of the art in 2015 that buffers should not be used for atropine solutions, as informed by the Remington reference Dr. Laskar calls the formulator's "bible," on the mistaken belief that the phosphate buffers listed in Akorn cannot buffer below a pH of 6.0. *See generally* Ex. 2003 ¶¶ 45–69. Remington, however, expressly lists phosphate salts in a suggested ophthalmic solution for atropine, but Dr. Laskar states, without support other than the Waterman reference, that "[n]either one of these phosphate salts, alone or in the disclosed combination, is a buffering agent to provide a pH of from about 4.8 to about 6.4. Nor do they provide, alone or in combination, a buffer for a solution having a pH no lower than 3.5 and no higher than 6.0." *Id.* ¶ 50.

As set forth above, we do not agree that the phosphate salts listed in Remington do not buffer at a pH of 6.0 or below. We do not understand Dr. Laskar's statement that these buffers also do not provide a pH from about 4.8 to about 6.4. Dr. Laskar testifies that it is difficult to change the

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pH of a solution by adjusting the ratio of acid to conjugate base of a buffer from a 50:50 ratio, *see* Ex. 2003 ¶ 59, and states that “[i]n Remington, for example, the atropine ophthalmic vehicle uses somewhat more than twice as much monobasic phosphate as dibasic phosphate on a molar basis, but this alters the pH only by about 0.3 pH units,” *id.* Dr. Laskar concludes, however, that the phosphate buffer system listed in claim 7 of the ’787 patent, the same buffering pair listed in Akorn, *can* provide a pH no greater than about 6.4 by utilizing “extremely large and counterintuitive variations from standard buffer protocols” to be able to “buffer near the limits of an agent’s buffering range.” *Id.* Patent Owner cannot have it both ways; phosphate buffers listed in Remington in the suggested atropine solution cannot be said to not buffer, while phosphate buffers listed in claim 7 of the ’787 patent, which do not have any particular amount or ratio of acid to base listed, do perform the function of a buffer that provides a pH of from about 4.8 to about 6.4.

We agree with Dr. Byrn that Remington does recommend the use of buffers to maintain the pH at the appropriate level. Ex. 1002 ¶ 50 (citing Ex. 1019, 52–54). In discussing ophthalmic preparations, Remington states:

Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. . . .

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimum for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

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It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability, but minimized so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily.

Ex. 1019, 54.

Remington is recommending a buffer to stabilize an ophthalmic solution for the product's shelf life, but also recommends a balance with the buffers capacity to prevent any resistance to adjustment by tear fluid when the ophthalmic solution is applied to the eye to provide patient comfort and compliance. Contrary to Dr. Laskar's testimony, the record evidence shows that buffers are recommended for ophthalmic solutions to maintain shelf life.

Akorn also discloses a pH range of 3.5 to 6.0 for its formulation that overlaps with the pH range at which atropine was known to be most stable, pH 3–5. Ex. 1002 ¶ 93; *see* Ex. 2003 ¶ 45 (Dr. Laskar admits that “The United States Pharmacopeia/National Formulary had long required atropine sulfate ophthalmic solution to be packaged for storage at a solution pH no greater than 6.0 and no less than 3.5.”). Patent Owner takes issue with the fact that we don't know the exact pH of Akorn's formulation. *See* Ex. 2003 ¶ 74. We don't find this argument persuasive as Akorn teaches a particular pH range for its formulation for 1% atropine, which informs a POSA of the appropriate pH range, if not a particular point within the range. The appropriate pH range set forth in Akorn overlaps with the claimed pH range in claim 1, and there is no dispute that pH is a result effective variable for the stability of an atropine solution and finding the optimum pH value for an

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atropine solution is within the level of ordinary skill of the art. *See* Ex. 1002 ¶¶ 96–98; Ex. 1005 (showing how to predict half-lives of atropine solutions at various pH values and temperatures); Ex. 2003 ¶¶ 38, 61; Ex. 1078, 143:11–144:5 (stating “a POSA would be able to prepare a buffer at pHs within that range of 4.8 to 6.4). This evidence is sufficient to support a case of obviousness. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence” of teaching away, unexpected results, or other pertinent evidence of nonobviousness.”).

Patent Owner also alleges criticality of the claimed pH range set forth in the claims when providing an overview of the ’787 patent. *See* PO Resp. 15–19; *see* Ex. 2003 ¶¶ 156–158. Patent Owner argues that the inventors discovered that “using a buffer was critical to atropine stability” for the claimed low dose in the claimed range. PO Resp. 18. This is not appropriate objective evidence of nonobviousness to rebut Petitioner’s proof of overlapping ranges between the prior art and the claimed pH range because regardless of whether the problem of the stability of atropine at low doses was unexpected, the result of using a buffer, pH stability for the range, was not unexpected. The buffer is just doing exactly what a buffer does as recognized: *viz.*, maintaining pH. *See* Ex. 1038, 2 (stating “primary purpose of a buffer is to control the pH of the solution”). The fact that the claimed range for a stable low dose atropine solution substantially overlapped with the USP stated range for atropine solutions is also not surprising or unexpected.

(3) Reason to Combine with a Reasonable Expectation of Success

The Petitioner asserts that a POSA would have been motivated to formulate lower-concentration formulations such as the claimed composition in claim 1 to reduce “the side effects without significant loss of efficacy.” Pet. 24 (citing Ex. 1002 ¶¶ 67–68). Recognizing the side effects of higher concentration atropine solutions, such as photophobia, cycloplegia, and mydriasis, causing poor patient compliance, Petitioner asserts that Chia studied lower dose atropine compositions and concluded that “a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.” *Id.* at 25 (citing Ex. 1002 ¶ 69; Ex. 1003, 1, 7, 8). This conclusion, Petitioner asserts would have motivated a POSA “to pursue a stable, ready-to-use formulation for that treatment.” *Id.* (citing Ex. 1003, 8; Ex. 1002 ¶¶ 71–72).

Petitioner further reasons that because using atropine to treat myopia requires long-term treatment, a POSA “would have been motivated to increase the stability and shelf life of low-concentration formulations.” Pet. 25 (citing Ex 1003, 1; Ex. 1002 ¶¶ 71–72). In light of the teachings of Kondritzer, Petitioner states that a POSA would have known that atropine’s stability was pH dependent, and “[i]n selecting a suitable buffer system for long-term stability of atropine solutions, a POSA would have looked to FDA-approved atropine ophthalmic solutions,” such as Akorn. Pet. 25–26 (citing Ex. 1005; Ex. 1002 ¶¶ 43–45, 74). In addition to shelf life, Petitioner asserts a POSA also would have been concerned about patient comfort and compliance with using the low-concentration atropine product and would know that the pH for optimum patient comfort is the same pH as tear fluid, about 7.4. *Id.* at 26–27. In balancing stability of atropine, which is most

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stable at a pH from 3 to 5 according to Kondritzer, Petitioner asserts that “a POSA would have been motivated to increase the long-term stability of *Chia*’s low-concentration atropine at pHs closer to the clinically desirable pH of 7.4.” *Id.* at 27 (citing Ex. 1002 ¶ 78). Petitioner asserts that a POSA would have had a reasonable expectation of success in doing so by using buffers, a common component in ophthalmic compositions, to target “the higher end of Akorn’s disclosed pH range in order to optimize stability in view of patient comfort” *Id.* at 27–28.

Patent Owner responds that the low-concentration atropine formulations did not contain buffers and that the state of the art in 2015 taught excluding the use of buffers. *See* PO Resp. 43–46. We have addressed Patent Owner’s argument that the state of the art in 2015 for ophthalmic solutions did not teach buffers. As we found above, the record evidence such as Remington shows that buffers are recommended for ophthalmic solutions to maintain shelf life.

We also note that the prior art references such as *Chia* described studies to determine the safety and efficacy of low-dose atropine solutions and were not commercially available formulations that must meet FDA requirements for safety and efficacy. *Chia* specifically states that “[a]tropine 0.01% is currently not commercially available.” Ex. 1003, 8.

Patent Owner also asserts that adding a buffer would decrease patient comfort by maintaining a low pH of the atropine solution when administered, causing increased tearing which would undermine efficacy by washing away the atropine. PO Resp. 46–48. We do not find this argument persuasive. As Remington explained, a POSA must choose a buffer to stabilize an ophthalmic solution, but also balance the shelf-life of the solution with a buffering capacity that allows a patient’s tears to easily

overcome an uncomfortable acidic pH of the ophthalmic solution. *See* Ex. 1019, 54. As Remington states, “[b]uffer capacity is the key,” and “buffer capacity should be adequate for stability, but minimized so far as possible to allow the overall pH of the tear fluid to be disrupted only momentarily.” *Id.* Buffering does not impede patient comfort when buffer capacity is properly assessed.

We agree with Petitioner and Dr. Byrn that “a POSA would have been motivated to formulate low-concentration atropine solutions that could be administered at pHs closer to those that provided optimal patient compliance and clinical efficacy, but that could also remain stable over long periods of time.” Ex. 1002 ¶ 78. We determine that Petitioner has shown an appropriate reason to combine the teachings of Chia, Akorn, and Kondritzer to arrive at the composition of claim 1 with a reasonable expectation of success.

(4) Conclusion

We determine that Petitioner has shown by a preponderance of the evidence that claim 1 of the ’787 patent would have been obvious over Chia, Akorn, and Kondritzer.

d) Dependent Claims 2, 4–9, and 12–19

Dependent claims 2, 4, and 5 each recite stabilized ophthalmic compositions with narrow ranges of atropine or atropine sulfate concentrations, i.e., claim 2—“from about 0.001 wt % to about 0.03 wt %,” claim 4—“from about 0.01 wt % to about 0.02 wt %,” claim 5—“about 0.01 wt %.” Petitioner relies on Chia’s teaching of 0.01% atropine, which is within claim 2’s range, at the lower end of claim 4’s range, and is the exact

amount as claimed in claim 5, to establish that these dependent claims would have been obvious as well. *See* Pet. 35–36 (citing Ex. 1002 ¶¶ 110–113).

Patent Owner does not address these additional limitations apart from its arguments as to claim 1. The reasons that we set forth above for the determination that claim 1 would have been obvious equally apply here. We determine that Petitioner has shown by the preponderance of the evidence on the record before us that claims 2, 4, and 5 would have been obvious over Chia, Akorn, and Kondritzer.

Claims 6 and 7 further define the buffering agent of claim 1 to include a phosphate buffering agent for claim 6 and “sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof” for claim 7, which Petitioner asserts Akorn teaches. *See* Pet. 36 (citing Ex. 1002 ¶¶ 116–117; Ex. 1004, 3). Patent Owner reasserts the same argument that it raised with respect to claim 1, namely, that Akorn does not teach the claimed phosphate buffers. *See* PO Resp. 57. We have addressed Patent Owner’s arguments with respect to claim 1 and found that Akorn does teach the claimed phosphate buffers.

Claim 8 further requires a tonicity adjusting agent, and claim 9 further defines the tonicity agent as a halide salt of a monovalent cation. Ex. 1001, 98:11–16. Petitioner asserts that “[a] POSA would have recognized that decreasing the concentration of atropine sulfate from *Akorn*’s 1% atropine sulfate solution to *Chia*’s 0.01% atropine sulfate solution would require the addition of a tonicity adjusting agent to maintain eye comfort” due to a reduction in the amount of salt in the solution. Pet. 37 (citing Ex. 1002 ¶¶ 122–124). Petitioner also asserts that sodium chloride, a halide salt of a monovalent cation, is a very common tonicity adjusting agent. *Id.* (citing Ex. 1002 ¶¶ 123–124; Ex. 1036, 1–3; Ex. 1019, 54).

Patent Owner responds that Petitioner has not shown that a reduction from 1% to 0.01% atropine sulfate will make enough difference in the osmolarity to be material to the tonicity of the solution, and Petitioner failed to account for the existing tonicity of Akorn's formulation. PO Resp. 56.

Dr. Byrn explains tonicity and that "isotonicity always is desirable and particularly is important in intraocular solutions." Ex. 1002 ¶ 122 (citing Ex. 1019, 54). Dr. Byrn then testifies that a reduction in the concentration of atropine sulfate, a salt, from 1% to 0.01 % would require a tonicity adjusting agent for eye comfort. *Id.* We credit Dr. Byrn's testimony as it is reasonable that a 100-fold decrease in the concentration of atropine sulfate in the solution would require some tonicity adjustment.

Patent Owner does not address the additional limitations of claims 12–18 apart from its arguments as to claim 1. Claims 12, 13, and 14 further require, respectively, a preservative, in a particular concentration, and a list of particular preservatives, which Chia and/or Akorn teach. *See* Pet. 38–39 (citing Ex. 1002 ¶¶ 126–132; Ex. 1003, 2; Ex. 1022 1–2; Ex. 1023, 1). Claim 15 further requires that the stabilized ophthalmic composition is "essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof," which Petitioner asserts is taught by the absence of these ingredients in Chia and Akorn. *See* Pet. 39 (citing Ex. 1002 ¶¶ 133–138; Ex. 1003; Ex. 1004, 3; Ex. 1019, 52). Claims 16 and 17 further require topical administration and instillation, respectively, which Petitioner asserts is taught by Chia and Akorn. *See* Pet. 40 (citing Ex. 1002 ¶¶ 139–143; Ex. 1003, 1; Ex. 1004, 1–4). Claim 18 further requires administering the atropine composition through an eye drop bottle, which Petitioner asserts is disclosed by Akorn. Pet. 41 (citing Ex. 1002 ¶¶ 144–148; Ex. 1004, 1–4).

We have reviewed Petitioner’s assertions in the Petition concerning claims 12–18 and Dr. Byrn’s testimony in support, and determine that Petitioner has shown by a preponderance of the evidence that these claims would have been obvious over Chia, Akorn, and Kondritzer.

Dependent claim 19 recites: “A method of treating the pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount of the stabilized ophthalmic composition of claim 1.” Ex. 1001, 98:52–57. Petitioner asserts that claim 19’s requirement for a method of treating is taught by Chia which found “that administration of its 0.01% atropine solution, via eyedrops, was effective to treat myopia and progression of myopia.” Pet. 41 (quoting Ex. 1003, 1).

Patent Owner raises similar arguments as it did for claim 1 that Chia was an unbuffered solution and that buffering decreased patient comfort. *See* Pet. 56–57. We have addressed these arguments with regard to claim 1 and find them unavailing here as well.

We determine that Petitioner has shown by a preponderance of the evidence that claim 19 would have been obvious over Chia, Akorn, and Kondritzer.

E. Remaining Grounds

Because we have determined that all challenged claims are unpatentable as obvious over Chia, Akorn, and Kondritzer, we need not reach the issue of whether these same claims are also unpatentable under Grounds 2 and 3. Therefore, we do not reach these grounds.

III. CONCLUSION¹⁶

For the foregoing reasons, we conclude Petitioner has shown by a preponderance of the evidence that claims 1, 2, 4–9, and 12–19 of the '787 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Patent Owner's Motion to Exclude Evidence is *denied*;

FURTHER ORDERED that claims 1, 2, 4–9, 12–19 of U.S. Patent No. 10,842,787 B2 have been shown by a preponderance of the evidence to be unpatentable under 35 U.S.C. § 103; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

In summary:

¹⁶ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

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Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1, 2, 4–9, 12–19	103	Chia, Akorn, Kondritzer	1, 2, 4–9, 12– 19	
1, 2, 4–9, 12–19	103	Chia, Akorn, Lund ¹⁷		
1, 2, 4–9, 12–19	103	Akorn, Wu, Kondritzer ¹⁸		
Overall Outcome			1, 2, 4–9, 12– 19	

¹⁷ Because we find these claims are unpatentable over Chia, Akorn, and Kondritzer, we do not determine their patentability under this ground.

¹⁸ Because we find these claims are unpatentable over Chia, Akorn, and Kondritzer, we do not determine their patentability under this ground.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EYENOVIA, INC.,
Petitioner,

v.

SYDNEXIS, INC.,
Patent Owner.

IPR2022-00414
Patent 10,940,145 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
Administrative Patent Judges.

MITCHELL, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Denying Patent Owner's Motion to Exclude
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

A. Background and Summary

On January 7, 2022, Eyenovia, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–7 and 11–20 of U.S. Patent No. 10,940,145 B2 (Ex. 1001, “the ’145 patent”). Paper 1, (“Petition” or “Pet.”). Sydnexis, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition on April 18, 2022. Paper 6 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to the Preliminary Response addressing the public accessibility of Exhibit 1004¹ and Patent Owner’s proposed claim construction for “buffer” and “buffering agent.” *See* Ex. 3001; Paper 7. Also, with our authorization, Patent Owner filed a Sur-reply in response. *See* Ex. 3001; Paper 8.

On July 15, 2022, we granted institution of an *inter partes* review of claims 1–7 and 11–20 of the ’145 patent on all grounds set forth in the Petition. *See* Paper 9 (“Dec.”) 2, 34.

Patent Owner filed a Response on October 21, 2022, *see* Paper 20 (“PO Resp.”), and Petitioner filed a Reply on January 13, 2023, *see* Paper 22 (“Reply”). Patent Owner filed its Sur-Reply on February 24, 2023. Paper 25 (“Sur-Reply”). An oral hearing was held on April 14, 2023, and a transcript of this hearing was entered into the record. Paper 37 (“Tr.”).

Patent Owner filed a Motion to Exclude Evidence on March 24, 2023. Patent Owner seeks to exclude Exhibit 1002, the Declaration of Dr. Byrn, Petitioner’s declarant, Exs. 1004 and 1057 constituting the Akorn labels, and Exhibits 1079 through 1088, Eyenovia’s Reply exhibits. Paper 30.

¹ Atropine Sulfate Ophthalmic Solution, USP 1%, NDA 206289 Product Label (July 2014) (Ex. 1004, “Akorn”).

Petitioner opposed the motion, *see* Paper 31, and Patent Owner filed a reply, *see* Paper 33. For the reasons set forth herein, the motion is *denied*.

This is a Final Written Decision under 35 U.S.C. § 318(a) as to the patentability of the challenged claims on which we instituted trial. Based on the complete record before us, we determine as set forth below that Petitioner has shown by a preponderance of the evidence that claims 1–7 and 11–20 of the ’145 patent are unpatentable.

B. Real Parties in Interest

The parties identify themselves as the real parties-in-interest. Pet. 62; Paper 4, 2; Paper 28, 2.

C. Related Matters

Petitioner states that they have filed petitions for *inter partes* review of related patents U.S. Patent No. 10,842,787 and U.S. Patent No. 10,888,557. Pet. 62. Petitioner further states that the ’145 patent issued from an application that is a continuation of U.S. Application No. 16/677,538, which in turn is a continuation of U.S. Application No. 15/568,381. *Id.* Petitioner avers that U.S. Application No. is a national phase application of International Application No. PCT/US2016/029222, which in turn is a continuation-in-part application of U.S. Application number 14/726,139 that issued as U.S. Patent No. 9,421,199 (“the ’199 patent”). *Id.* According to Petitioner, the ’199 patent was challenged in IPR2021-00439 by Nevakar, Inc. *Id.* at 62–63. Petitioner states that IPR2021-00439 and other petitions filed by Nevakar, Inc. were terminated due to settlement prior to institution. *Id.* at 63.

Patent Owner identifies IPR2022-00384 and IPR2022-00415 as related matters. Paper 4, 2; Paper 28, 2.

D. The '145 Patent

The '145 patent relates to ophthalmic compositions for the treatment of an ophthalmic disorder, such as pre-myopia, myopia, or the progression of myopia. Ex. 1001, 5:7–11. The '145 patent explains that muscarinic antagonists, such as atropine, prevent or arrest the development of myopia in humans. *Id.* at 9:52–58.

The '145 patent states that the clinical use of atropine for therapy had been limited due to side effects, such as glare from pupillary dilation and blurred vision. *Id.* at 12:23–26. The Specification attributes these effects to high concentrations of atropine (e.g., 1 wt% or higher). *Id.* at 12:26–31. The Specification explains also that some muscarinic antagonist compositions were formulated with lower pH values (e.g., less than 4.5) to promote stability of the muscarinic antagonist. *Id.* at 10:5–9. Lower pH values, however, cause discomfort or other side effects, such as pain or a burning sensation in the eye, which can be prevented or alleviated by formulating muscarinic antagonist compositions at higher pH ranges. *Id.* at 10:9–13.

According to the '145 patent, “there is a need for a stabilized ophthalmic composition with extended shelf life upon storage” and there is a need for stabilizing such a composition by arresting or reducing hydrolysis of at least some of its active agents. *Id.* at 9:47–52. In view of this, the Specification contemplates low concentrations of ophthalmic agents (e.g., from about 0.0001 wt% to about 0.5 wt%). *Id.* at 12:32–37. For instance, the '145 patent describes ophthalmic compositions that include from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist, such as atropine or atropine sulfate, and water. *Id.* at 6:64–66, 7:5–6. The '145 patent describes pH values for the ophthalmic compositions (e.g., less than about 7.3) and

that the compositions have a certain potency after a period of time under storage conditions. *Id.* at 7:13–38. Additionally, the ’145 patent states that the ophthalmic compositions may include a buffer agent. *Id.* at 7:57–58.

E. Illustrative Claims

Petitioner challenges claims 1–7 and 11–20 of the ’145 patent. Claim 1 is the only independent claim. For this Final Written Decision, independent claim 1 (set forth below with bracketed letters to identify specific limitations for ease of reference) is illustrative of the claimed subject matter.

1. 1[a] A kit comprising:
 - 1[b] a. a vial comprising a pharmaceutical composition, the pharmaceutical composition comprising:
 - 1[c] i. about 0.01 mg/g to about 0.5 mg/g of atropine or atropine sulfate;
 - 1[d] ii. water; and
 - 1[e] iii. a buffer; and
 - 1[f] b. instructions for use.

Ex. 1001, 99:12–19.

Dependent claims 2 and 3 provide additional limitations to further refine the range for the amount of atropine or atropine sulfate of claim 1. *See* Ex. 1001, 99:20–27. Dependent claims 4 and 5 further defines the buffer of claim 1. *See id.* at 99:28–35. Dependent claim 6 further requires a tonicity agent, and dependent claim 7 further defines the tonicity agent. *See id.* at 99:36–39. Dependent claims 10–14 has further requirements for preservative in the composition. *See id.* at 100:4–17. Dependent claim 15 further requires the composition to be free of procaine and benactyzine (*see id.* at 100:17–19); dependent claims 16 through 18 further requires

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particular pH ranges for the composition (*see id.* at 100:20–25); dependent claim 19 further requires the composition be a solution (*see id.* at 100:26–27); and dependent claim 20 further requires the composition be sterile (*see id.* at 100:28–29).

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–7 and 11–20 would have been unpatentable on the following grounds:

Claims Challenged	35 U.S.C. §²	Reference(s)/Basis
1–7 and 11–20	103	Chia, ³ Akorn ⁴
1–7 and 11–20	103	Akorn, Wu ⁵

Petitioner also relies upon the Declaration of Stephen Byrn, Ph.D. (Ex. 1002). Patent Owner relies upon the Declaration of Paul A. Laskar, Ph.D. (Ex. 2003).

² The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the ’145 patent issued has an effective filing date after that date, the AIA version of § 103 applies.

³ Audrey Chia et al., *Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)*, 119 OPTHALMOLOGY 347–54 (2012) (Ex. 1003, “Chia”).

⁴ Atropine Sulfate Ophthalmic Solution, USP 1%, NDA 206289 Product Label (July 2014) (Ex. 1004, “Akorn”).

⁵ WO 2014/182620 A1, published November 13, 2014 (Ex. 1006, “Wu”).

II. ANALYSIS

A. *Principles of Law*

1. *Burden*

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016 (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”))). Therefore, in an *inter partes* review, the burden of proof is on the Petitioner to show that the challenged claims are unpatentable, and that burden never shifts to the patentee. *See* 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).

2. *Obviousness*

To ultimately prevail in its challenge to Patent Owner’s claims, Petitioner must demonstrate by a preponderance of the evidence⁶ that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains

⁶ The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

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(“POSA” or “POSITA”). *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In determining obviousness when all elements of a claim are found in various pieces of prior art, “the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success.” *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also WMS Gaming, Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) (“When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references.”). “Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 1381 (finding a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.”) (internal quotations and citations omitted).

An obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in

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the art would employ.” *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. Section 103 “bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. *KSR*, 550 U.S. at 399 (stating that obviousness is determined against the backdrop of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the art). Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also*

Orthopedic Equip. Co. v. U.S., 702 F.2d 1005, 1011 (Fed. Cir. 1983)
(quoting with approval *Jacobson Bros.*).

Petitioner asserts that “[a] person of ordinary skill in the art (‘POSA’) at the time of the purported invention would have had a Ph.D. in chemistry, organic chemistry, physical chemistry, or pharmaceuticals, with several years of experience preparing and/or testing pharmaceutical formulations.” Pet. 20 (citing Ex. 1002 ¶¶ 61–62). Petitioner further contends that “[a] POSA would have been familiar with common inactive ingredients used in aqueous pharmaceutical formulations and the basic characteristics of aqueous formulations such as stability, and would have had knowledge about drug degradation kinetics.” *Id.*

Patent Owner asserts that a narrower definition of a POSA should be employed—one that includes expertise in ophthalmic formulation. PO Resp. 4.⁷ Patent Owner states that Petitioner’s declarant, Dr. Byrn, has “extremely limited experience with ophthalmic formulation,” which “calls into serious question whether he is qualified to opine on the perspective of a POSA in the relevant field.” *Id.* at 5.

We do not agree with Patent Owner that the level of ordinary skill in the art should be limited to experience with ophthalmic formulation. The claims at issue generally require a kit with a vial of a pharmaceutical composition of atropine, water, and buffer, and instructions for use. *See* Ex. 1001, 99:12–19 (claim 1). As Dr. Byrn points out, the technology surrounding use of atropine, a nonselective muscarinic antagonist, to treat myopia, has been extensively studied for over a hundred years and is known

⁷ Although Patent Owner disagrees with Petitioner’s definition of a POSA, Patent Owner does not provide its own definition apart from including expertise in ophthalmic formulation. *See* PO Resp. 4–7.

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as “the oldest and most effective pharmacological treatment to inhibit the development of myopia.” *See* Ex. 1002 ¶ 26 (quoting Ex. 1008, 1) (citing Ex. 1003, 1; Ex. 1012, 2). The degradation of atropine is also well known to primarily result from cleavage of the acyl-oxygen bond during ester hydrolysis, *see id.* ¶ 43 (citing Ex. 1017, 1; Ex. 1024, 5), with the rate of acid-catalyzed reaction being much slower than that of the base-catalyzed reaction, leading to stability of atropine at a lower pH range ($\text{pH} < \sim 3$), *see id.* ¶ 45 (citing Ex. 1005, 1,4–5). Concerning specifically the use of atropine in the eye, Dr. Byrn points out that it is well known that ophthalmic solutions should be “formulated to be sterile, isotonic and buffered for stability and comfort.” *See* Ex. 1002 ¶ 47 (quoting Ex. 1019, 52) (noting Ex. 1019, 54 (pH of tear fluid is 7.4)).

None of this chemistry concerning the stability of atropine or its administration in the eye is remarkable or not well understood by a POSA as defined by Petitioner. *See* PO Resp. 10 (stating “the stability of atropine was understood to be a ‘predictable function,’ and a ‘routine matter,’ of temperature and solution pH”), 40–41 (same). We see no reason why someone with drug formulation experience, but not specific experience with ophthalmic solutions, would not qualify as a POSA. Therefore, we continue to apply Petitioner’s definition of a POSA in this final written decision.

C. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 100(b) (2019). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*,

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415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioner states that “[f]or the purposes of this proceeding only, Petitioner does not believe that any claim terms need to be construed.” Pet. 21. Patent Owner “agrees that the claims should be understood according to their ordinary and customary meaning.” PO Resp. 25. In reply, Petitioner asserts that the ordinary meaning of “about” is “approximately,” and the ordinary meaning of “buffering agent” or “buffer” “is nothing more than an excipient that helps control pH.” Reply 2. Petitioner asserts that Patent Owner agrees with the definition of “buffering agent” and “buffer” by stating that “[t]he patent uses terms buffer and buffering in their normal sense, which entails providing pH control or maintenance.” *Id.* (quoting PO Resp. 28).

Based upon our review of the evidence of record, we determine that no claim terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (Only those terms that are in controversy need be construed, “and only to the extent necessary to resolve the controversy.”). Insofar as the parties dispute whether Akorn discloses a buffer, we address those contentions in our discussion below of the challenged claims.

D. Obviousness over Chia and Akorn

Petitioner asserts that claims 1–7 and 11–20 would have been obvious over the combined teachings of Chia and Akorn. Pet. 22–41. In addition to challenging the public availability of Akorn, Patent Owner disagrees and states that the Akorn reference “does not disclose the phosphate salts make a buffer. Nor does it disclose that the Akorn product has a pH range of 3.5–6.0. Each of these failures is case-dispositive.” PO Resp. 1.

1. Chia (Ex. 1003)

Chia is a journal article that describes two studies regarding the treatment of myopia using atropine eyedrops. Ex. 1003, 1. In the first study, “Atropine for the Treatment of Myopia 1” (“ATOM1”), it was shown that atropine 1% eyedrops were effective in controlling myopic progression but with visual side effects resulting from cycloplegia and mydriasis. *Id.* The second study described in Chia, “Atropine for the Treatment of Myopia 2” (“ATOM2”), compared the efficacy and visual side effects of 3 lower doses of atropine: 0.5%, 0.1%, and 0.01%. *Id.* The authors of Chia conclude “[a]tropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression.” *Id.*

Chia notes that atropine, a nonspecific muscarinic antagonist, at 1.0% and 0.5% has been shown to be effective in slowing myopia progression, but its safety profile regarding pupil size and accommodation was a concern. Ex. 1003, 6. Chia states:

Every unit increase in pupil size results in an exponential increase in the amount of light entering the eye, and this can cause glare and potential phototoxicity. Atropine also decreases

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accommodation amplitude and near vision so that children may require bifocal or progressive glasses to read. The ideal atropine dose would be one with the best balance between efficacy and safety.

Id.

To explore the ideal atropine dose, Chia performed the ATOM2 study using 0.01% atropine as a potential control due to its assumed minimal effect. Ex. 1003, 7. Chia found that “contrary to expectations, atropine 0.01% also had significant clinical effects as evidence by its effect on myopia progression, accommodation, and pupil size.” *Id.* In comparing the 0.01% atropine dose to the 0.5% and the 0.1% doses, Chia found “the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared with the 0.5% group. Likewise, the difference in axial length increase was statistically larger than in both the 0.1% and 0.5% groups. However, absolute differences between groups were clinically small” *Id.* Chia did note that no other atropine 0.01% studies were available for direct comparison, but Chia did compare the data to a study⁸ testing 0.05% atropine and a study⁹ testing 0.025% atropine. *Id.*

Although Chia found that “[o]verall, atropine-related adverse effects were uncommon at the 0.01% dose . . . [t]here are no long-term studies on the effect of atropine on the eye, and continued vigilance is necessary. However, atropine has been clinically available since the early 1900s, and so

⁸ Lee et al., *Prevention of myopia progression with 0.05% atropine solution*, 22 J. OCUL. PHARACOL. THER. 41–46 (2006) (Ex. 1012, “Lee”).

⁹ Fang et al., *Prevention of myopia onset with 0.025% atropine in premyopic children*, 26 J. OCUL PHARMOCOL. THER. 341–345 (2010) (Ex. 1013, “Fang”).

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far there are no known long-term adverse effects associated with its use.”

Ex. 1003, 7. Chia states:

In conclusion, our results suggest that 0.5%, 0.1%, and 0.01% atropine remain effective in reducing myopia progression, compared with placebo treatment, and that the clinical differences in myopia progression among these 3 groups are small. The lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while attaining a clinically significant improved safety profile in terms of accommodation, pupil size, and near visual acuity, and subsequently reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer adverse events. Atropine 0.01% is currently not commercially available. However, these findings collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.

Id. at 7–8.

2. *Akorn (Ex. 1004)*

Petitioner identifies Exhibit 1004 as a product label for Akorn Atropine Care, which appears to be an excerpt from New Drug Application 206289. *See* Pet. vi; Ex. 1004, 1. Akorn describes a 1% atropine sulfate ophthalmic solution for topical application to the eye. Ex. 1004, 1. Akorn explains that atropine is an anti-muscarinic agent that is indicated for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia. *Id.* at 1, 2. Akorn explains atropine’s mechanism of action as follows:

The pupillary constrictor muscle depends on muscarinic cholinergic activation. This activation is blocked by topical atropine resulting in unopposed sympathetic dilator activity and mydriasis. Atropine also weakens the contraction of the ciliary

muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate such that the eye cannot focus for near vision.

Id. at 4. Akorn describes applying 1 drop of the solution to the cul-de-sac of the conjunctiva forty minutes prior to an intended maximum dilation time.

Id.

Akorn explains that the solution contains atropine sulfate as an active ingredient. *Id.* at 3. Akorn further describes the following inactive ingredients: “benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.” *Id.*

3. Analysis

For its assertion that claims 1–7 and 11–20 would have been obvious over the combined teachings of Chia and Akorn, Petitioner relies on Akorn as teaching a buffer as part of the pharmaceutical composition of claim 1. Pet. 32. Patent Owner challenges Petitioner’s reliance on Akorn asserting that the Petition fails to prove that Akorn was publicly available prior to the undisputed critical date of April 23, 2015, which Patent Owner also raised in its Preliminary Response. *See* PO Resp. 55–58; Prelim. Resp. 28–30. Patent Owner also challenges the testimony of Dr. Byrn in its Motion to Exclude Evidence asserting that “Dr. Byrn’s proffered opinions exceed his expertise, are not based on ‘scientific knowledge,’ ‘sufficient facts or data,’ and are not ‘the product of reliable principles’ and methods ‘reliably applied’ to the facts of this case.” Paper 30, 2 (“Mot. to Exclude”).

Because the prior art status of Akorn and Dr. Byrn’s testimony is relevant to all grounds asserted by Petitioner, we begin our discussion with these issues.

a) Prior Art Status of Akorn (Ex. 1004)

Petitioner has the burden to prove Akorn qualifies as prior art. *See In re Magnum Oil Tools*, 829 F.3d at 1376. “[A]t the institution stage, the petition must identify, with particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication.” *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 (“Hulu”) at 13 (PTAB Dec. 20, 2019) (precedential).

“Public accessibility” is considered to be “the touchstone in determining whether a reference constitutes a ‘printed publication’ bar under 35 U.S.C. §102(b).” *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). “A given reference is ‘publicly accessible’ upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.” *SRI Int’l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

A determination whether a particular reference qualifies as a printed publication “is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis.” *Hall*, 781 F.2d at 899. In a proceeding before the Board, there is no presumption in favor of finding that a reference is a printed publication. *Hulu*, Paper 29 at 16.

During the institution phase of this proceeding, we authorized further briefing on the issue of whether Akorn was publicly accessible before the critical date, and each party filed a brief addressing this issue. *See* Ex. 3001; Paper 7; Paper 8. In our Institution Decision, we addressed the parties’

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arguments and determined on the record before us at that time that “Petitioner has adequately shown for institution that Akorn was sufficiently accessible to the public interested in the art and searchable on the DailyMed website such that a POSA could have found it with reasonable diligence.” Dec. 24. In making this determination, we examined Petitioner’s additional evidence, Exhibit 1057, that it submitted with its reply to the preliminary response, and determined “that Petitioner properly relies on Exhibit 1057 as additional evidence to confirm that Exhibit 1004 was published and publicly accessible in July of 2014.” *See* Dec. 24.

In making this determination, we made the following findings concerning Exhibit 1057 for purposes of institution.

In particular, on the current record, we find that Petitioner’s Exhibit 1057 provides persuasive corroboration for its contention that Akorn was publicly accessible in July of 2014. Exhibit 1057 includes printouts of webpages from “DailyMed.” Ex. 1057. In the “ABOUT DAILYMED” section on the first page of the exhibit, there is a statement explaining that “The National Library of Medicine (NLM)’s DailyMed searchable database provides the most recent labeling submitted to the Food and Drug Administration (FDA) by companies and currently in use (i.e., ‘in use’ labeling).” *Id.* at 1. Among other items, the DailyMed “contains labeling for prescription and nonprescription drugs for human and animal use.” *Id.* The statement also explains that “[t]he NLM provides DailyMed to the public” and “[t]he labeling on DailyMed is typically reformatted to make them easier to read.” *Id.*

On the third page of Exhibit 1057, there is a copy of the DailyMed “LABELING ARCHIVES” webpage which depicts a “Labeling Archives Search,” with a first field for entering a drug name, and a second field for entering a date. *Id.* at 3. The webpage explains that “[t]his archive allows the user to retrieve the label current for a given date.” *Id.* Search results for the term “ATROPINE SULFATE” on “07/31/2014” are displayed. *Id.* There is an indication that the search provided 135 results which

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are listed in a row, apparently over a number of webpages. *Id.* The results are organized with the “DATE POSTED” identified in one column, along with the term “download” which appears to be formatted as a web link, and the “DRUG NAME” identified in a second column, wherein the drug name listed appears to be formatted as a web link. *Id.* Below the drug name, the name of the “Packager” is identified, along with a “Version” number. *Id.* Petitioner draws our attention to the label identified with July 24, 2014, as the “DATE POSTED,” “Atropine (atropine sulfate) solution/drops,” as the “DRUG NAME,” Akorn, Inc. as the “Packager,” with the “Version” noted as “7.” *Id.*

We understand the next page of the exhibit to be a copy of the DailyMed webpage depicting the version 7 label for Akorn’s atropine sulfate that was posted on July 24, 2014. Ex. 1057, 4. Based on our review, but for minor web-related formatting differences, this label posted on DailyMed appears to be the same as the label depicted in Exhibit 1004. In particular, we observe that both labels: (a) refer to “HIGHLIGHTS OF PRESCRIBING INFORMATION” for “Atropine Sulfate Ophthalmic Solution, USP 1% for topical application to the eye;” (b) include the “Revised: 7/2014” statement; (c) include the same indications and usage, dosage and administration; (d) set forth the same sections/subsections; and (e) describe the contents of the drug in the same manner, including the statement identifying inactives as: “benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.” *Compare* Ex. 1004, 1–5, *with* Ex. 1057, 4–6.

Taken together, we find that the evidence relied on in the Petition, i.e., Exhibits 1004, 1020, 1021, along with Exhibits 1056, 1058, and especially, 1057, submitted with the Reply, provide strong indicia that the July 2014 version of Akorn’s atropine sulfate drug label represented on the current record as Exhibit 1004 was posted on July 24, 2014, on the DailyMed website. We do not find any dispute on the current record that DailyMed is a federal government website that is accessible to the public and presented in a manner that allows the public to readily search its database for drug labels that have been

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approved by the FDA. Moreover, as Petitioner asserts, the DailyMed website explains, “The DailyMed RSS feed provides updates and information about new drug labels approved by the FDA and published on NLM’s DailyMed Web site.” Ex. 1057, 1. In other words, the DailyMed website further extends its reach to the public through such feed.

Dec. 20–23.

Patent Owner in its Response continues to question the public availability of Akorn. *See* PO Resp. 56–58. Patent Owner continues to assail the public availability of Akorn as shown by the exhibits originally presented with the Petition, *see id.*, but we agreed with some of these criticisms. For instance, we stated:

To begin, we note that, in some respects, we agree with Patent Owner’s position. For example, we agree with Patent Owner that the “7/14” revision date printed on Akorn, on its own, indicates only that some unknown author(s) modified the document on that date. *See* Prelim. Resp. 29, PO Sur-reply 2–3. Indeed, similar to the copyright or creation dates in *Hulu*, the revision date, by itself, is insufficient to demonstrate that the exhibit was publicly available on that date. *See Hulu*, Paper 29 at 19. We also agree with Patent Owner that neither the FDA approval date of the Akorn atropine sulfate drug product nor the sale or use of that product demonstrates the public accessibility of drug label reflected in Akorn prior to the critical date. *See* Prelim. Resp. 30, PO Sur-reply 2–3.

Dec. 20. Our decision on the public availability of Akorn turned on the additional evidence Petitioner submitted as Exhibit 1057. *See id.*

The only criticism Patent Owner presents with reference to our analysis of Exhibit 1057 as set forth above is to question a statement on the DailyMed webpage concerning when filtering by published date was added to Web Services. *See* PO Resp. 57–58; Sur-Reply 25. Patent Owner states: “But Petitioner’s DailyMed exhibit (created on September 15, 2021) acknowledges that ‘Filtering by Published Date [Was] Added to Web

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Services’ only as late as October 2015 (EX1057, 1, 2), which falls after the critical date. EX1001, Cover. As the very same search means that Petitioner used to find the label in EX1057 admittedly did not exist before the critical date, Petitioner has failed to demonstrate pre-critical date public availability of this new label.” PO Resp. 57.

We find that Patent Owner’s criticism misses the mark. Petitioner is using the DailyMed exhibit as further evidence that Akorn was publicly available as of the revision date of 7/2014 as shown on Akorn, Ex. 1004. *See* Opp. to Mot. to Exclude 8 (“Moreover, public records from DailyMed, part of the NIH’s National Library of Medicine, show that EX1004 was posted publicly on that site at least by July 24, 2014. *See* EX1057, 3.”) As set forth in the Petition, EX1004, a drug label to Akorn, bears July 2014 revision dates that comport with its FDA approval and publication well before the critical date. *See* Pet., 10–22; *Hulu*, 13. It also bears Akorn’s corporate insignia. EX1004, 5. Additional evidence confirms these dates are reliable. EX1056-58.”); 3 (“Public records from DailyMed, part of the NIH’s National Library of Medicine, show that EX1004 was posted publicly on **July 24, 2014.**”). Whether a POSA could have searched this way for labels published before the critical date is irrelevant; Petitioner is only using the evidence to show that Akorn was, in fact, published in July 2014, before the critical date on a searchable website. *See id.* Patent Owner does not dispute that DailyMed was searchable by drug name, which would be the logical way a POSA would search such a database for information for a drug of interest.

Petitioner also provides further evidence that the Akorn label was published on July 24, 2014, through a response by the National Library of Medicine (“NLM”) to a Freedom of Information Act request. *See* Ex. 1071.

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In this Freedom of Information Act request, Petitioner asked for written confirmation that the substance of the Akorn label was posted on July 24, 2014, on the DailyMed website. *Id.* The National Institutes of Health (“NIH”) responded that version 7 of the Akorn label was published on DailyMed on July 24, 2014, and provided the URL that is reflected in the Akorn label in Exhibit 1057 from the DailyMed website. *See* Ex. 1072, 6; Ex. 1057, 4–7. NIH also confirmed that NLM “received version 7 of this label from the FDA on 07/24/2014 @ 2:15:04 PM,” “published version 7 on DailyMed on the same day, 07/24/2014 @ 14:59:48 PM,” and confirmed that “NLM does not make changes to the content contained within any SPL [or structured product labeling] records that it receives from the FDA.” Ex. 1072, 6. We find that Petitioner has provided more than sufficient evidence that the Akorn label reflected in Ex. 1004 was publicly available before the critical date.

For the reasons set forth above, we determine that Petitioner has shown by a preponderance of the evidence that Akorn, Ex. 1004, is a printed publication that was publicly available before the critical date.

b) Patent Owner’s Motion to Exclude Evidence

Patent Owner moves to exclude from evidence the Declaration of Dr. Byrn (Ex. 1002), Exhibits 1004 and 1057 that constitute the Akorn labels, and Exhibits 1079 through 1088 that Petitioner submitted with its Reply. Mot. to Exclude 2. Petitioner filed an Opposition (Paper 31, “Opp. to Mot. to Exclude”), and Patent Owner filed a Reply (Paper 33, “Reply to Mot. to Exclude”). For the following reasons, Patent Owner’s Motion to Exclude is *denied*.

Pursuant to our Rules, a motion to exclude evidence must be filed to preserve any previously-made objections to evidence. 37 C.F.R. § 42.64(c). The motion must identify where in the record the objections were made, and must explain the objections. *Id.* Patent Owner appropriately identifies where in the record it previously served objections to the exhibits it seeks to exclude. Mot. to Exclude 2 (citing Papers 12, 23).

As the moving party, Patent Owner bears the burden of proof to establish that it is entitled to the requested relief, i.e., the exclusion of evidence as inadmissible under the Federal Rules of Evidence (“FRE”). *See* 37 C.F.R. §§ 42.20(c), 42.64(a).

(1) Dr. Byrn’s Testimony (Ex. 1002)

Patent Owner challenges Dr. Byrn’s testimony under FRE 702 as not based on sufficient “scientific knowledge,” not based on “sufficient facts or data,” and not “the product of reliable principles” and methods “reliably applied” to the facts of this proceeding. Mot. to Exclude 2.

(a) Requisite Scientific Knowledge

For instance, although Dr. Byrn agrees that the ’145 patent is “directed to the field of ophthalmic compositions and ophthalmic solutions,” Patent Owner asserts that Dr. Byrn’s curriculum vitae (Ex. 1002, Appendix A) “provides no indication that Dr. Byrn has any expertise in ophthalmic formulation.” Mot. to Exclude 2–3 (citing Ex. 2009, 97:19–98:14, 104:20–106:5). Patent Owner further states:

During his deposition, Dr. Byrn identified brief eyedrop forays (none significant enough to merit mention in his CV or declaration), but could not identify any ophthalmic product he formulated before the critical date. Even as of 2021, Dr. Byrn never had primary responsibility for formulating any drug

product that has received regulatory approval or been commercialized.

Mot. to Exclude 3 (citing Ex. 2010 ¶ 8). Patent Owner also criticized Dr. Byrn’s alleged lack of knowledge of ophthalmic terms such as lacrimation. *See id.*

Petitioner responds that the primary focus in evaluating the admissibility of testimony under FRE 702 is “whether an expert’s opinion will assist the trier of fact,” a low bar, and many of Patent Owner’s criticisms go to the weight to be accorded Dr. Byrn’s testimony rather than its admissibility. Opp. to Mot. to Exclude 1–7. In applying FRE 702, Petitioner asserts that “Dr. Byrn, a professor of medicinal chemistry who specializes in drug formulation, is eminently qualified to opine about the straightforward formulation issues presented in this proceeding.” *Id.* at 1.

Petitioner asserts that Patent Owner does not contest that Dr. Byrn meets Petitioner’s POSA definition (as we have determined should be applied in this proceeding), but even if we required experience in formulating ophthalmic pharmaceuticals, we find that Dr. Byrn has such experience. *See* Opp. to Mot. to Exclude 2–6; *see* Ex. 1002, Appendix A ¶¶ 3–10. Petitioner asserts that Dr. Byrn testifies:

That he worked as a consultant for Alcon—a well-known eye care company—on a number of ophthalmic products, including ones that were FDA-approved, prior to the critical date. *See* Ex. 2009, 136:12–137:12. He further testified that he worked with eye drops as part of Purdue’s Africa program. *Id.* at 49:149–50:2.

Opp. to Mot. to Exclude 4. Petitioner also asserts that Dr. Byrn accurately described the term “lacrimation” in his deposition. *Id.* at 4 n.2 (citing Ex. 2009, 49:11–14; Ex. 1002 ¶ 75 (quoting Ex. 1047, 2)).

As we have previously determined, a POSA need not have specific experience in ophthalmic formulation. *See* Section II.B. Dr. Byrn has ample experience to qualify as a POSA, which we defined as a person having a Ph.D. in chemistry, organic chemistry, physical chemistry, or pharmaceuticals, with several years of experience preparing and/or testing pharmaceutical formulations at the time of the purported invention. *See* Section II.B.; Ex. 1002 ¶¶ 3–10. Dr. Byrn has the requisite academic background, as well as extensive experience in drug development and formulation. *See* Ex. 1002 ¶¶ 3–10. Dr. Byrn testifies that his “laboratory has done extensive research on drug formulations, and [he has] authored over two hundred book chapters and peer-reviewed journal articles on properties of a wide variety of pharmaceutical compositions.” *Id.* ¶ 10.

We also find, however, that Dr. Byrn has experience with ophthalmic formulations. Dr. Byrn testifies that he has “worked quite a bit with eyedrops” in Purdue’s Africa program. Ex. 2009, 49:21–24. In his Declaration, Dr. Byrn testifies that he was a co-founder of the Sustainable Medicines in Africa in the Kilimanjaro and Arusha regions of Tanzania in 2007. Ex. 1002 ¶ 5. Dr. Byrn describes this program more extensively in his curriculum vitae as providing educational programs that are “aimed at providing source of well-trained manufacturing scientists for pharmaceutical industry in Tanzania and Africa,” and including a GMP-level pharmaceutical manufacturing facility to teach manufacturing under strict quality control, as well as a quality medicines laboratory equipped with HPLCs. Ex. 1002, Appendix, 82. Dr. Byrn also testifies that he consulted with Alcon on a number of ophthalmic drug products although he was not primarily responsible for their formulation. *See* Ex. 2009, 136:12–20.

We find Dr. Byrn’s alleged lack of “primary” responsibility for the formulation of an ophthalmic product to be somewhat of a red herring in assessing whether Dr. Byrn has “expertise in ophthalmic formulation” as Patent Owner asserts should be required. *See* Mot. to Exclude 2–3. In response to questions about whether Dr. Byrn ever had primary responsibility for formulating a drug product that has received regulatory approval, Dr. Byrn testifies that he has “been on a team that formulated drug products for both for commercial sale and IND testing.” Ex. 2009, 134:19–24. Dr. Byrn also pointed out what he considered to be a false premise in the questions related to “primary” responsibility for drug formulation. Dr. Byrn testifies:

I have been a consultant on a large number of products that came on the market and I worked in a team, and my work was – part of the work was critical for certain specifications and certain marketing steps, but I don’t believe that in this day and age a person is primarily responsible for bringing a drug on the market; it’s a team activity.

Id. at 135:15–23. We credit Dr. Byrn’s testimony here.¹⁰ We also determine that Dr. Byrn satisfies the requirements for a POSA as we have determined it should be defined, without specific expertise in ophthalmic formulation, but also determine that even if we applied Patent Owner’s heightened standard requiring such expertise, Dr. Byrn satisfies that

¹⁰ We also find that Dr. Byrn was clearly familiar with the term “lacrimation,” which means “the secretion of tears especially when abnormal or excessive,” but chose to use the word “tearing” instead. *See* Ex. 2009, 49:3–14; *see also* <https://www.merriam-webster.com/dictionary/lacrimation> (accessed June 25, 2023) (defining lacrimation).

definition also. Dr. Byrn has the requisite scientific knowledge to serve as an expert for Petitioner.

(b) Sufficiency of Underlying Facts and Data; Reliability of Principles and Methods as Applied to Underlying Facts and Data

Patent Owner asserts that Dr. Byrn's alleged inexperience with ophthalmic formulations led him to offer an opinion not based on sufficient facts or data or reliable principles, *i.e.*, that Dr. Byrn's opinion that "Akorn teaches the uses of buffering agents to achieve a solution pH range of 3.5 to 6.0 were 'premised' on an undisclosed assumption that the buffering range of the weak acid extends ± 2 pH units away from its pK_a ." Mot. to Exclude 4 (citing PO Resp. 36–37; Ex. 2009, 96:5–97:4; Ex. 1002 ¶¶ 20, 24, 65, 79, 96, 137, 150, 159). Patent Owner also asserts Dr. Byrn's assumption has been shown to be incorrect in a district court proceeding in which he testified. *See* Mot. to Exclude 4–7.

Petitioner counters that Dr. Byrn's opinions are based on sufficient facts and data and are reliable. Opp. to Mot. to Exclude 5–6. As an example, Petitioner points to Dr. Byrn's reliance on Remington (Ex. 1019), which Dr. Laskar admits is a formulator's "bible," to establish that "Remington means exactly what it says: buffer capacity represents a compromise between stability and comfort, and thus a buffer with diminished capacity (*e.g.*, the one provided by sodium phosphate salts) should be used." Opp. to Mot. to Exclude 5 (citing Ex. 2003 ¶¶ 62–63; Ex. 1002 ¶ 49).

Petitioner also points to support for Dr. Byrn's opinion that sodium phosphate salts "can still buffer outside of ± 1 unit away from their pK_a " in the "reliable scientific literature that Patent Owner seeks to preclude the Board from considering." *Id.* at 6 (citing Exs. 1079–1083 (buffer recipes

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using the claimed sodium phosphate salts below pH 6.0)). Finally, Petitioner asserts that Dr. Byrn's testimony in the district court proceeding is inapposite because

The primary legal issue in that case dealt with infringement under the doctrine of equivalents, and whether a generic company's "proposed product contains an equivalent to the 'buffer' of the claims[.]" *See* Ex. 2010, 2. Unlike here, the alternative excipient that the generic company contended was a buffer had not be identified, disclosed, and claimed as such by the patentee. *See* Ex. 1001 (claim 5).

Opp. to Mot. to Exclude 6–7.

We agree with Petitioner here that Patent Owner's concerns about the sufficiency of the support for Dr. Byrn's opinions goes more to the weight to be accorded such opinions rather than a need to exclude such opinions. *See* TPG 40–41, 79 ("A motion to exclude must explain why the evidence is not admissible (e.g., relevance or hearsay) but may not be used to challenge the sufficiency of the evidence to prove a particular fact."). We also note that the findings in the district court litigation are based on a different record that is not before us here. For instance, the district court relies on a Lewis reference and a Harris reference that is not before us and testimony from Dr. Richard Moreton that is also not before us here. *See* Ex. 2010 ¶¶ 63–69. Therefore, we determine that the district court's findings are not sufficiently probative of the questions before us here.

Also, the district court's findings are not as definitive as Patent Owner states. The patent owner in the district court case attempted to prove infringement by the doctrine of equivalents for a formulation that did not expressly contain a buffer, but that it argued inherently contained a buffer from the chemical disassociation of the active ingredient in the product. *See* Ex. 2010, 64–65. The district court found that patent owner failed to prove

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that this actually occurs in the accused product. *Id.* at 65. The district court case is in stark contrast with the underlying facts of this proceeding in which the prior art formulation expressly contains the same buffers as claimed in the '145 patent. *See* Ex. 1001, 99:33–35 (claim 5); Ex. 1004, 3.

(c) Conclusion

Based on the foregoing, we *deny* Patent Owner's motion to exclude Exhibit 1002, Dr. Byrn's testimony.

(2) The Akorn Labels (Exs. 1004 and 1057)

Patent Owner asserts that Exhibits 1004 and 1057 should be excluded because Petitioner failed to show that Exhibit 1004 (Akorn) was publicly available before the critical date, and Exhibit 1057 is deficient to show such public availability of Exhibit 1004. Mot. to Exclude 7–8.

We have previously addressed these issues in our determination of the prior art status of Akorn, Ex. 1004, set forth above. *See* Section II.D.3.a). For these same reasons, we *deny* Patent Owner's motion to exclude Exhibits 1004 and 1057.

(3) Exhibits 1079–1088

Patent Owner moves to exclude Exhibits 1079 through 1088 submitted with Petitioner's Reply. *See* Mot. to Exclude 2, 8–15. Patent Owner asserts that these exhibits should have been submitted with the Petition and are untimely. *Id.* at 8. Patent Owner also asserts that Dr. Byrn did not “elect to submit a Reply declaration, rely upon any of these documents, or testify that any of them are the kinds of documents an expert in his field (much less a POSA in the field of the invention) would rely upon.” *Id.*

Petitioner asserts that these documents were presented to Dr. Laskar at his deposition to rebut Patent Owner’s assertions that “two common buffering agents, sodium dihydrogen phosphate and disodium hydrogen phosphate—identified and claimed by the ’145 patent as buffering agents—are not buffers in the claimed range.” Opp. to Mot. to Exclude 10 (citing PO Resp. 34; Ex. 2003 ¶ 56).

Our Trial Practice Guide states that:

Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability. A party may also submit rebuttal evidence in support of its reply.

Patent Trial and Appeal Board Consolidated Trial Practice Guide 73 (Nov. 2019) (citing *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1077–78 (Fed. Cir. 2015)).

Here, we find that Exhibits 1079 through 1088 are appropriate rebuttal evidence. Petitioner uses these exhibits to test Dr. Laskar’s opinions concerning the buffering range for sodium dihydrogen phosphate and disodium hydrogen phosphate. *See generally* Ex. 1078, 91–189.¹¹ As the Federal Circuit noted in *Belden*, there is no bright-line demarcation between support for Petitioner’s prima facie case and rebuttal evidence. For instance, the Federal Circuit stated that using rebuttal evidence as support for the prima facie case does not necessarily mean that it was “necessary” for the prima facie case requiring it to be in the Petition.

¹¹ In response to Patent Owner’s Objections to Evidence, Petitioner also provided a Declaration of Rebecca L. Baker, a Research Analyst at the law firm representing Petitioner, attesting to the authenticity of Exhibits 1079, 1081–1085. *See* Ex. 1095.

Evidence admitted in rebuttal to respond to the patent owner's criticisms will commonly confirm the prima facie case. That does not make it necessary to the prima facie case. And nothing required the Board to write its opinion to separate the material offered by [petitioner] at different stages of the proceeding.

See Belden, 805 F.3d at 1079.

For these reasons, we *deny* Patent Owner's motion to exclude Exhibits 1079 through 1088.

c) Claim 1

Petitioner asserts that claim 1 recites a kit with two core elements previously known in *Chia* and *Akorn*: “(1) a low-concentration atropine formulation as taught by *Chia*, combined with (2) any number of well-known buffering agents to stabilize the atropine formulation, including by using pH levels known to be desirable for treating myopia.” Pet. 22.

Petitioner describes what it terms the “ample” motivation to make such a combination and the reasonable expectation of success for such a combination as follows. *See* Pet. 23 (citing Ex. 1002 ¶¶ 64–78).

In 2012, *Chia* disclosed that low-concentration atropine eye drops effectively treated myopia and improved patient compliance issues associated with higher concentration compositions. Ex. 1003, 1. Thus, *Chia*'s clinical success would have provided motivation to make and use low-concentration atropine formulations. Because atropine's pH-dependent stability was well known in the art, and overly acidic pH was known to cause eye discomfort, a POSA would have been motivated to buffer the composition in order to achieve the optimal pH levels for patient comfort and stability.

Well aware of *Akorn*'s use of a pH range of 3.5–6.0 for its 1% atropine solution, a POSA would have been motivated to try and use *Akorn*'s buffering system to achieve the same pH range for *Chia*'s low-concentration atropine solution. Ex. 1002 ¶¶ 73–77. A POSA would have confirmed via routine experimentation

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that using a buffer to achieve this range was appropriate. *Id.* As shown in *Kondritzer*^[12] and *Lund*,^[13] a POSA would have known of clear empirical and theoretical teachings regarding the stability of aqueous atropine solutions at varying pHs and temperatures.

Pet. 22–23.

Patent Owner responds that Akorn “does not disclose the phosphate salts make a buffer. Nor does it disclose that the Akorn product has a pH range of 3.5–6.0. Each of these failures is case dispositive,” as all grounds rely exclusively on Akorn to disclose its alleged “‘buffer system’ (allegedly the phosphate salts) and an alleged pH range of 3.5–6 for the Akorn product.” PO Resp. 1, 25. Patent Owner also asserts that Petitioner’s only motivation for making the claimed combinations in the ’145 patent results from improper hindsight. *See* PO Resp. 46–52.

(1) Limitations 1[a], 1[b], 1[c], 1[d], and 1[f]

We begin our analysis with the limitations of claim 1 that Patent Owner does not dispute are taught by the prior art. Petitioner points to both Chia and Akorn as teaching the preamble of claim 1, 1[a] a kit, assuming it is limiting. Pet. 28–29; *see* Ex. 1002 ¶¶ 82–85; *see also* Ex. 1001, 69:60–64 (describing kits comprising one or more disclosed ophthalmic compositions and instructions for using the kit). Petitioner points to where in Akorn it teaches an ophthalmic composition comprising atropine or atropine sulfate and instructions for use of this composition. Pet. 28 (citing Ex. 1004, 1–2 (“In individuals from three (3) months of age or greater, 1 drop topically to

¹² Kondritzer et al., *Stability of Atropine in Aqueous Solution*, J. AM. PHARM. ASSOC. 46(9):531–535 (1957) (Ex. 1005, “Kondritzer”).

¹³ Lund et al., *The Kinetics of Atropine and Apotatropine in Aqueous Solutions*, ACTA CHEM. SCAND. 22:3085–3097 (1968) (Ex. 1007, “Lund”).

the cul-de-sac of the conjunctiva, forty minutes prior to the intended maximal dilation time. In individuals 3 years of age or greater, doses may be repeated up to twice daily as needed.”)). Petitioner also points to Chia as teaching an ophthalmic composition of atropine or atropine sulfate with instructions for use for participants in the study that were “randomized to receive 0.5%, 0.1%, or 0.01% atropine once nightly in both eyes” Pet. 28–29 (citing Ex. 1003, 2). From these disclosures, Dr. Byrn testifies that a POSA would “have understood that *Chia* and *Akorn* describe ‘kits’ within the meaning of the ’145 patent and render the preamble obvious.” Ex. 1002 ¶ 85.

We agree with Dr. Byrn’s assessment of the teachings of Chia and Akorn in light of the disclosure of the ’145 patent concerning kits and credit his testimony.

Petitioner relies on Chia and Akorn for teaching limitation 1[b]: “a vial comprising a pharmaceutical composition.” Pet. 29–30. Petitioner notes that both Chia and Akorn disclose containers, of which vial is one type, and states that: “First, *Chia* discloses that its composition was ‘prepackaged’ in ‘bottles.’ Ex. 1003, 2. Second, *Akorn* discloses that its composition ‘is supplied in a plastic dropper bottle.’ Ex. 1004, 5.” Pet. 29. Dr. Byrn also testifies that it was common practice to use vials to store atropine pharmaceutical compositions, and opined that “using a vial as an alternative container to store the compositions of *Chia* and/or *Akorn* would have been obvious to a POSA.” Ex. 1002 ¶ 88 (citing Ex. 1024, 2; Ex. 1053, 2).

Based on this evidence presented by Petitioner, we credit Dr. Byrn’s testimony that it would have been obvious to a POSA to use a vial to store the atropine solutions of Chia and Akorn.

Petitioner relies on Chia to teach limitation 1[c], which requires the pharmaceutical composition to have “about 0.01 mg/g to about 0.5 mg/g of atropine or atropine sulfate.” Pet. 30–31. Petitioner asserts that “*Chia*’s aqueous 0.01% atropine solution falls squarely within [this] claimed range . . . [rendering] this limitation obvious.” Pet. 30 (citing Ex. 1003, 1; Ex. 1002 ¶ 90).

We agree with Petitioner that the overlap between the concentration of Chia’s atropine solution and the claimed range establishes a prima facie case of obviousness, for which Patent Owner has not offered any rebuttal. *See Genentech, Inc. v. Hospira Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020) (citing *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)).

Petitioner relies on both Chia and Akorn to teach limitation 1[c] requiring water. Pet. 31–32. Petitioner points to Akorn’s disclosure of one of its inactive ingredients for its atropine sulfate composition is water. *Id.* at 31 (citing Ex. 1004, 3; Ex. 1018, 4–5). Dr. Byrn notes that “[i]t is common for pharmaceutical compositions containing atropine to use water as an inactive ingredient.” Ex. 1002 ¶ 93 (citing Ex. 1018, 4–5).

Petitioner also relies on Chia’s disclosure of 0.01% atropine formulated as “eye drops,” along with the understanding in the art that “eye drops are commonly aqueous ophthalmic solutions,” to teach limitation 1[c]. Pet. 31 (citing Ex. 1003, 1–2; Ex. 1034, 1).

Dr. Byrn testifies that:

In view of that common knowledge, a POSA would have understood that *Chia*’s eye drops were an aqueous solution (i.e. a solution where the solvent is water). *See* Ex. 1054, 39 (defining “aqueous solution” as a “solution with the solvent as water.”). Thus, a POSA would have understood that the ophthalmic compositions in *Chia* and *Akorn* comprised water, as claimed by limitation 1[d].

Ex. 1002 ¶ 94.

We credit Dr. Byrn’s testimony in light of the evidence presented that a POSA would recognize that both ophthalmic compositions in Chia and Akorn comprised water.

For limitation 1[f] requiring “instructions for use,” Petitioner points to Akorn’s instructions for application of its pharmaceutical composition, *see* Ex. 1004, 1–2, as well as Chia’s instructions, *see* Ex. 1003, 2. Dr. Byrn opines based on these disclosures that “a POSA would have understood that both *Chia* and *Akorn* disclose ‘instructions for use.’” Ex. 1002 ¶ 99. We credit Dr. Byrn’s testimony here in light of the teachings of Chia and Akorn.

(2) Limitation 1[e]

The heart of the parties’ dispute in this case involves whether the cited art teaches limitation 1[e] that requires a buffer. *See* Pet. 32; PO Resp. 25–40.

Petitioner relies on Akorn, asserting it discloses several buffers, including dibasic sodium phosphate and monobasic sodium phosphate. Pet. 32. Patent Owner disagrees. *See* PO Resp. 25–40.

Patent Owner asserts that “all grounds critically hinge on using the same ‘buffer system’ and pH range allegedly disclosed in [Akorn].” PO Resp. 29. But, Patent Owner asserts that Akorn does not state that it employs a buffering agent to control or maintain pH of its atropine solution, and does not even disclose the actual pH of its solution. *Id.* at 25. Patent Owner also asserts that the Akorn does not disclose that the phosphate salts made a buffer, and could not have buffered Akorn’s solution at the listed pH range. *Id.* at 1, 29. Dr. Laskar testifies that in listing the pH range of 3.5 to 6.0, Akorn is merely showing compliance with the pH limits imposed by the

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National Formulary of the U.S. Pharmacopeia (“USP”) and does not state the pH of the described solution. PO Resp. 1, 32–33. Patent Owner also asserts that “[t]he fact that there is zero overlap between the buffering range of the phosphates as reported in the Waterman reference Petitioner relied upon and the USP pH limits incorporated into [Akorn] provides another sufficient reason to reject Petitioner’s argument that the unspecified amount of phosphate in [Akorn] satisfies the claimed buffer limitation.” *Id.* at 33–34.

Akorn describes the ingredients of its formulation as follows.

Each mL of Atropine Sulfate Ophthalmic Solution USP, 1% contains: **Active:** atropine sulfate 10 mg equivalent to 8.3 mg of atropine. **Inactives:** benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium Hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.

Ex. 1004, 3.

Patent Owner’s argument rests on a listed buffering range in the Waterman reference for phosphoric acid that does not encompass a pH of 3.5 to 6.0 as set forth in Akorn. *See* Ex. 2003 ¶ 52; Ex. 1040, 23. As Dr. Laskar testifies, “Waterman Table 8 lists the ‘Buffering Range’ of Phosphoric acid as ‘2–3.1, 6.2–8.2.’” Ex. 2003 ¶ 52 (citing Ex. 1040, Table 8). Dr. Laskar testifies:

As the Waterman reference submitted with the petition explains, when selecting a buffer, which acts to maintain a solution pH (e.g., at the pH of maximum stability of the active ingredient), the “primary criteria for selection” are “the pH range and buffer capacity [which is maximal at a pH value equal to the pK_a of the buffer (164)] for the buffer.” Ex. 1040, 23 (bracketed in material in original). Waterman states that its “Table 8 lists commonly used buffers along with their pK_a values and optimal pH ranges.”

Id., Table 8; *see also* paragraph 9 above. In other words, the buffering range of phosphoric acid and its dibasic sodium phosphate and monobasic sodium phosphate salts does not cover or even overlap with a solution of pH of 3.5–6.

Ex. 2003 ¶ 52.

Patent Owner’s argument presumes that the pK_a for a particular buffer is set at a particular pH range which is not malleable depending on the conditions of the solution that is being buffered. Waterman itself refutes this presumption. First, Waterman describes the buffering ranges listed in Table 8 as “optimal” pH ranges of $pK_a \pm 1$ indicating some buffering capacity may exist below or above the given ranges. *See* Ex. 1040, 23. Dr. Byrn testifies that the most effective pH range for a buffer is within ± 1 of its pK_a , but “[i]t’s not a hard cutoff; it’s an effectiveness issue.” Ex. 2009, 87:5–12; *see id.* at 88:23–89:19 ($pK_a \pm 1$ covers the most effective buffer range, but it is not a hard cutoff), 91:7–18 (person of skill knows $pK_a \pm 1$ is not a hard cutoff); 95:11–97:4 (applying the Henderson, Hasselbach equation provides a wider pH buffering range than $pK_a \pm 1$). Dr. Laskar testifies that pK_a changes as a function of temperature. Ex. 1078, 124:5–9. Waterman also states that “[u]se of co-solvents, surfactants, and complexing agents to solubilize a drug may also influence that buffering capacity and final pH of a formulation by altering the effective pK_a of the buffer and/or directly interacting with the buffer components.” Ex. 1040, 24. The evidence of record indicates that the pK_a for a buffer is not static, but depends on the parameters of the solution in which the buffer is used.

As for the specific phosphate buffers used in Akorn and claim 5 of the ’145 patent, Petitioner submitted credible evidence that the lower end of the buffer range for these buffers may be as low as pH 5.4. For instance, in Chapter 4 of the Fifth Edition of the European Pharmacopoeia, with which

Dr. Laskar testifies he is familiar and which contains recipes for various buffer solutions, is described a 0.067 molar phosphate buffer solution with a pH of 5.4 that is within the 3.5 to 6.0 pH range set forth in Akorn. *See* Ex. 1081, 6; Ex. 1078, 113:12–118:20; *see also* Ex. 1078, 115:22–116:5 (stating European Pharmacopoeia provides a recipe for an 0.067 molar phosphate buffer solution pH 5.4 within the 3.5 to 6.0 pH range).

Petitioner also presents further evidence of a phosphate buffer with a pH range of 5.8 to 8.0 as set forth in a book titled “Buffers: A guide for the preparation and use of buffer in biological systems,” by Calbiochem, an affiliate of Merck KGaA. *See* Ex. 1082, 1, 2, 25. The excerpt showing the recipe is set forth in a screenshot, which is reproduced below. Ex. 1082, 25.

6. Phosphate Buffer; pH range 5.8 to 8.0

(a) 0.1 M Sodium phosphate monobasic; 13.8 g/l (monohydrate, M.W. 138.0)

(b) 0.1 M Sodium phosphate dibasic; 26.8 g/l (heptahydrate, M.W. 268.0)

Mix sodium phosphate monobasic and dibasic solution in the proportions indicated and adjust the final volume to 200 ml with deionized water. Adjust the final pH using a sensitive pH meter.

ml of Sodium phosphate, Monobasic	92.0	81.5	73.5	62.5	51.0	39.0	28.0	19.0	13.0	8.5	5.3
ml of Sodium phosphate, Dibasic	8.0	18.5	26.5	37.5	49.0	61.0	72.0	81.0	87.0	91.5	94.7
pH	5.8	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0

The screenshot above shows a recipe and accompanying table for making an aqueous phosphate buffer having a pH between 5.8 and 8.0 by mixing 0.1 M sodium phosphate monobasic with 0.1 M sodium phosphate dibasic in deionized water.

Petitioner further presents evidence from PubChem from the National Institutes of Health on the pK_a values for Monosodium phosphate and disodium hydrogen phosphate. *See* Exs. 1084, 1085. The first publication lists the pK_a for monosodium phosphate as a range from 6.8–7.2 “depending

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on the physiochemical characteristics during pK_a determination.” Ex. 1084, 7. The second publication lists the pK_a ’s for disodium hydrogen phosphate in the following table, which differ from those set forth in the Waterman reference. Ex. 1085, 8.

3.2.13 Dissociation Constants

$pK_{a1} = 2.15$; $pK_{a2} = 6.83$; $pK_{a3} = 12.38$ (phosphoric acid), all at 25 °C

Sigma-Aldrich; Sodium phosphate dibasic. S9763. Sigma-Aldrich, St. Louis, MO. Available from, as of Nov 30, 2006: <https://www.sigmaaldrich.com/catalog/search/ProductDetail/SIAL/S9763>

The table is table 3.2.13 from the PubChem listing for Disodium hydrogen phosphate, showing pK_a values for dissociation of 2.15, 6.83, and 12.38 at 25° C.

With this record evidence in mind, we turn to what a POSA would glean from reviewing Akorn. Dr. Byrn testifies that Akorn discloses standard buffering agents, including dibasic sodium phosphate, also known as disodium hydrogen phosphate, and monobasic sodium phosphate, also known as sodium dihydrogen phosphate, that have been shown in the evidence just discussed to be able to buffer Akorn’s formulation at least in the upper part of the cited pH range. Ex. 1002 ¶ 96 (citing Ex. 1019, 52; Ex. 1026, 4–5). We disagree with Dr. Laskar’s reliance solely on the Waterman reference as disclosing a buffering range for phosphate salts that “has no overlap with a solution pH of 3.5 to 6.0,” and do not credit his conclusion that a POSA would understand this lack of overlap “to completely contradict Dr. Byrn’s assertions that these phosphate salts represent a ‘common buffer’ that was used in EX1004 ‘to maintain a pH of 3.5 to 6.0.’” See Ex. 2003 ¶ 78.

We do not agree with Dr. Laskar’s criticism that Akorn does not disclose buffers. See Ex. 2003 ¶¶ 71–72. Dr. Laskar testifies that Akorn does not disclose any buffers. *Id.* Dr. Laskar further testifies:

To the contrary, the disclosure of EX1004 is consistent with the direction provided in Remington and the state of the art in 2015 regarding atropine aqueous ophthalmic solutions. Everything I have read in EX1004 is consistent with the state of the art before 2015, which was to avoid using a buffer or buffering agent in the acidic solution of storage within the boundaries (pH 3.5–6.0) imposed by the USP.

Ex. 2003 ¶ 71.

We find, however, that Dr. Laskar’s statements concerning the state of the art in 2015, including about the teachings of the Remington reference, are not sufficiently supported by record evidence. For instance, Dr. Laskar premises his conclusion concerning the state of the art in 2015 that buffers should not be used for atropine solutions, as informed by the Remington reference Dr. Laskar calls the formulator’s “bible,” on the mistaken belief that the phosphate buffers listed in Akorn cannot buffer below a pH of 6.0. *See generally* Ex. 2003 ¶¶ 45–69. Remington, however, expressly lists phosphate salts in a suggested ophthalmic solution for atropine, but Dr. Laskar states, without support other than the Waterman reference, that “[n]either one of these phosphate salts, alone or in the disclosed combination, is a buffering agent to provide a pH of from about 4.8 to about 6.4. Nor do they provide, alone or in combination, a buffer for a solution having a pH no lower than 3.5 and no higher than 6.0.” *Id.* ¶ 50.

As set forth above, we do not agree that the phosphate salts listed in Remington do not buffer at a pH of 6.0 or below. We do not understand Dr. Laskar’s statement that these buffers also do not provide a pH from about 4.8 to about 6.4. Dr. Laskar testifies that it is difficult to change the pH of a solution by adjusting the ratio of acid to conjugate base of a buffer from a 50:50 ratio, *see* Ex. 2003 ¶ 59, and states that “[i]n Remington, for example, the atropine ophthalmic vehicle uses somewhat more than twice as

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much monobasic phosphate as dibasic phosphate on a molar basis, but this alters the pH only by about 0.3 pH units,” *id.* Dr. Laskar concludes, however, that the phosphate buffer system listed in claim 7 of the ’787 patent (or claim 5 of the ’145 patent), the same buffering pair listed in Akorn, *can* provide a pH no greater than about 6.4 by utilizing “extremely large and counterintuitive variations from standard buffer protocols” to be able to “buffer near the limits of an agent’s buffering range.” *Id.* Patent Owner cannot have it both ways; phosphate buffers listed in Remington in the suggested atropine solution cannot be said to not buffer, while phosphate buffers listed in claim 7 of the ’787 patent or claim 5 of the ’145 patent, which do not have any particular amount or ratio of acid to base listed, do perform the function of a buffer that provides a pH of from about 4.8 to about 6.4.

We agree with Dr. Byrn that Remington does recommend the use of buffers to maintain the pH at the appropriate level. Ex. 1002 ¶ 50 (citing Ex. 1019, 52–54). In discussing ophthalmic preparations, Remington states:

Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. . . .

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimum for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer

capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability, but minimized so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily.

Ex. 1019, 54.

Remington is recommending a buffer to stabilize an ophthalmic solution for the product's shelf life, but also recommends a balance with the buffers capacity to prevent any resistance to adjustment by tear fluid when the ophthalmic solution is applied to the eye to provide patient comfort and compliance. Contrary to Dr. Laskar's testimony, the record evidence shows that buffers are recommended for ophthalmic solutions to maintain shelf life.

Akorn also discloses a pH range of 3.5 to 6.0 for its formulation that overlaps with the pH range at which atropine was known to be most stable, pH 3–5. Ex. 1002 ¶ 133; *see* Ex. 2003 ¶ 45 (Dr. Laskar admits that “The United States Pharmacopeia/National Formulary had long required atropine sulfate ophthalmic solution to be packaged for storage at a solution pH no greater than 6.0 and no less than 3.5.”). Patent Owner takes issue with the fact that we don't know the exact pH of Akorn's formulation. *See* Ex. 2003 ¶ 74. We don't find this argument persuasive as Akorn teaches a particular pH range for its formulation for 1% atropine, which informs a POSA of the appropriate pH range, if not a particular point within the range.

The appropriate pH range set forth in Akorn overlaps with the claimed pH ranges in dependent claims 16, 17, and 18, and there is no dispute that pH is a result effective variable for the stability of an atropine solution and finding the optimum pH value for an atropine solution is within the level of ordinary skill of the art. *See* Ex. 1002 ¶¶ 96–98; Ex. 1005 (showing how to

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predict half-lives of atropine solutions at various pH values and temperatures); Ex. 2003 ¶¶ 38, 61, 62; Ex. 1078, 143:11–144:5 (stating “a POSA would be able to prepare a buffer at pHs within that range of 4.8 to 6.4). This evidence is sufficient to support a case of obviousness. *See E.I. DuPont de Nemours, Inc. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence” of teaching away, unexpected results, or other pertinent evidence of nonobviousness.”).

Patent Owner alleges criticality of the claimed pH range set forth in the claims when providing an overview of the ’145 patent. *See* PO Resp. 15–18; Ex. 2003 ¶¶ 156–158. Patent Owner argues that the inventors discovered that “using a buffer was critical to atropine stability” for the claimed low dose in the claimed range. PO Resp. 18. This is not appropriate objective evidence of nonobviousness to rebut Petitioner’s proof of overlapping ranges between the prior art and the claimed pH range because regardless of whether the problem of the stability of atropine at low doses was unexpected, the result of using a buffer, pH stability for the range, was not unexpected. The buffer is just doing exactly what a buffer does as recognized: *viz.*, maintaining pH. *See* Ex. 1038, 2 (stating “primary purpose of a buffer is to control the pH of the solution”). The fact that the claimed range for a stable low dose atropine solution substantially overlapped with the USP stated range for atropine solutions is also not surprising or unexpected.

(3) Reason to Combine with a Reasonable Expectation of Success

The Petitioner asserts that a POSA would have been motivated to formulate lower-concentration formulations such as the claimed composition in claim 1 “to reduce patient side effects while still effectively treating myopia.” Pet. 24 (citing Ex. 1002 ¶¶ 64–72). Recognizing the side effects of higher concentration atropine solutions, such as photophobia, cycloplegia, and mydriasis, causing poor patient compliance, Petitioner asserts that Chia studied lower dose atropine compositions and concluded that “a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.” *Id.* (citing Ex. 1002 ¶ 69; Ex. 1003, 1, 7, 8). This conclusion, Petitioner asserts would have motivated a POSA “to pursue a stable, ready-to-use low-concentration atropine formulation for treating myopia.” *Id.* at 24–25 (citing Ex. 1003, 1; Ex. 1002 ¶¶ 70–72).

Petitioner further reasons that because using atropine to treat myopia requires long-term treatment, a POSA “would have been motivated to formulate a low-concentration atropine pharmaceutical composition with an increased stability and shelf-life.” Pet. 25 (citing Ex. 1003, 1; Ex. 1002 ¶¶ 71–72). In light of the teachings of Kondritzer, Petitioner states that a POSA would have known that atropine’s stability was pH dependent, and “[i]n selecting a suitable buffer system for long-term stability of atropine solutions, a POSA would have looked to FDA-approved atropine ophthalmic solutions,” such as Akorn. Pet. 25 (citing Ex. 1005; Ex. 1002 ¶¶ 43–45, 74, 76).

In addition to shelf life, Petitioner asserts a POSA also would have been concerned about patient comfort and compliance with using the low-concentration atropine product and would know that the pH for optimum

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patient comfort is the same pH as tear fluid, about 7.4. *Id.* at 26. In balancing stability of atropine, which is most stable at a pH from 3 to 5 according to Kondritzer, Petitioner asserts that “a POSA would have been motivated to increase the long-term stability of *Chia*’s low-concentration atropine at pHs closer to the clinically desirable pH of 7.4.” *Id.* at 26 (citing Ex. 1002 ¶ 75–77). Petitioner asserts that a POSA would have had a reasonable expectation of success in doing so by using buffers, a common component in ophthalmic compositions, to target “the higher end of Akorn’s disclosed pH range in order to optimize stability in view of patient comfort . . .” *Id.* at 27.

Patent Owner responds that the low-concentration atropine formulations did not contain buffers and that the state of the art in 2015 taught excluding the use of buffers. *See* PO Resp. 40–43. We have addressed Patent Owner’s argument that the state of the art in 2015 for ophthalmic solutions did not teach buffers. As we found above, the record evidence such as Remington shows that buffers are recommended for ophthalmic solutions to maintain shelf life.

We also note that the prior art references such as *Chia* described studies to determine the safety and efficacy of low-dose atropine solutions and were not commercially available formulations that must meet FDA requirements for safety and efficacy. *Chia* specifically states that “[a]tropine 0.01% is currently not commercially available.” Ex. 1003, 8.

Patent Owner also asserts that adding a buffer would decrease patient comfort by maintaining a low pH of the atropine solution when administered, causing increased tearing which would undermine efficacy by washing away the atropine. PO Resp. 43–45. We do not find this argument persuasive. As Remington explained, a POSA must choose a buffer to

stabilize an ophthalmic solution, but also balance the shelf-life of the solution with a buffering capacity that allows a patient's tears to easily overcome an uncomfortable acidic pH of the ophthalmic solution. *See* Ex. 1019, 54. As Remington states, “[b]uffer capacity is the key,” and “buffer capacity should be adequate for stability, but minimized so far as possible to allow the overall pH of the tear fluid to be disrupted only momentarily.” *Id.* Buffering does not impede patient comfort when buffer capacity is properly assessed.

We agree with Petitioner and Dr. Byrn that “a POSA wishing to make a kit for myopia treatment would have been motivated to select a suitable buffer system, such as *Akorn*'s, to maintain solution pH and atropine stability throughout the life of the low-concentration atropine pharmaceutical composition.” Ex. 1002 ¶ 77. We determine that Petitioner has shown an appropriate reason to combine the teachings of *Chia* and *Akorn* to arrive at the composition of claim 1 with a reasonable expectation of success.

(4) Conclusion

We determine that Petitioner has shown by a preponderance of the evidence that claim 1 of the '145 patent would have been obvious over *Chia* and *Akorn*.

d) Dependent Claims 2–7 and 11–20

Dependent claims 2 and 3 each recite kits with narrower ranges of atropine or atropine sulfate concentrations than that in claim 1. *See* Ex. 1001, 99:20–27. Petitioner asserts that “*Chia*'s aqueous 0.01% atropine solution falls squarely within the claimed ranges of ‘about 0.01 mg/g to about 0.3 mg/g or from about 0.1 mg/g to about 0.2 mg/g’ of claim 2, and

the claimed ranges of ‘about 0.1 mg/g, about 0.2 mg/g, about 0.25 mg/g, about 0.3 mg/g, about 0.4 mg/g, or about 0.5 mg/g’ of claim 3.” Pet. 33–34.

We agree with Petitioner that the overlap between the concentration of Chia’s atropine solution and the claimed ranges of claims 2 and 3 establish a prima facie case of obviousness, for which Patent Owner has not offered any rebuttal. *See Genentech*, 946 F.3d at 1341. Thus, we find that Petitioner has shown by a preponderance of the evidence that claims 2 and 3 would have been obvious over Chia and Akorn.

Claims 4 and 5 further define the buffer of claim 1 including “a phosphate buffering agent” in claim 4 and “sodium dihydrogen phosphate and disodium hydrogen phosphate” in claim 5, which Petitioner asserts is taught by Akorn’s disclosure of “two phosphate buffering agents: dibasic sodium phosphate (i.e., disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate).” Pet. 34 (citing Ex. 1004, 3); Ex. 1001, 99:28–35. Patent Owner reasserts the same argument that it raised with respect to claim 1, namely, that Akorn does not teach the claimed phosphate buffers. *See* PO Resp. 54–55. We have addressed Patent Owner’s arguments with respect to claim 1 and found that Akorn does teach the claimed phosphate buffers.

Claim 6 further requires a tonicity adjusting agent, and claim 7 further defines the tonicity agent as a halide salt of a monovalent cation. Ex. 1001, 99:36–39. Petitioner asserts that “[a] POSA would have recognized that decreasing the concentration of atropine sulfate from *Akorn*’s 1% atropine sulfate solution to *Chia*’s 0.01% atropine sulfate solution would require the addition of a tonicity adjusting agent to maintain eye comfort,” due to a reduction in the amount of salt in the solution. Pet. 35 (citing Ex. 1002 ¶¶ 114–117). Petitioner also asserts that sodium chloride, a halide salt of a

monovalent cation, is a very common tonicity adjusting agent. *Id.* (citing Ex. 1002 ¶¶ 115–117; Ex. 1036, 1–3; Ex. 1019, 54).

Patent Owner responds that Petitioner has not shown that a reduction from 1% to 0.01% atropine sulfate will make enough difference in the osmolarity to be material to the tonicity of the solution, and Petitioner failed to account for the existing tonicity of Akorn’s formulation. PO Resp. 54.

Dr. Byrn explains tonicity and that “isotonicity always is desirable and particularly is important in intraocular solutions.” Ex. 1002 ¶ 114 (citing Ex. 1019, 54). Dr. Byrn then testifies that a reduction in the concentration of atropine sulfate, a salt from 1% to 0.01 % would require a tonicity adjusting agent for eye comfort. *Id.* We credit Dr. Byrn’s testimony as it is reasonable that a 100-fold decrease in the concentration of atropine sulfate in the solution would require some tonicity adjustment.

Dependent claims 16 through 18 require an acidic pH, a pH of from about 3.8 to about 6.4, and a pH of less than 5, respectively. Ex. 1001, 100:20–25. Petitioner relies on the pH range listed in Akorn, pH 3.5 to 6.0 as overlapping with the pH ranges required by claims 16–18. *See* Pet. 38. Patent Owner again argues that Akorn does not disclose the pH of the solution and “does not disclose that the Akorn product is formulated across a pH range of 3.5 to 6.0, but merely that it does not violate USP pH limitations,” it does not disclose overlapping ranges with those in claims 16–18. PO Resp. 52–53. As we have previously stated, we don’t agree with Patent Owner’s position here because Akorn teaches a particular pH range for its formulation for 1% atropine, which informs a POSA of the appropriate pH range, if not a particular point within the range.

Patent Owner does not address the additional limitations of claims 11–15, 19, or 20 apart from its arguments as to claim 1. Claims 11 through

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14 further require a preservative, in particular concentrations, and a list of particular preservatives, which Chia and/or Akorn teach. *See* Pet. 36–37 (citing Ex. 1002 ¶¶ 118–124; Ex. 1003, 2; Ex. 1004, 3; Ex. 1022, 1–2; Ex. 1023, 1). Claim 15 further requires that the stabilized ophthalmic composition is “essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof,” which Petitioner asserts is taught by the absence of these ingredients in Chia and Akorn. *See* Pet. 37–38 (citing Ex. 1002 ¶¶ 125–130; Ex. 1003; Ex. 1004, 3; Ex. 1019, 52). Claim 19 requires that the pharmaceutical composition is a solution, and claim 20 requires that the pharmaceutical composition is sterile, which Petitioner asserts is taught by Akorn and/or Chia. Pet. 40–41 (citing Ex. 1002 ¶¶ 140–147; Ex. 1003, 1, 2; Ex. 1004, 1–4).

We have reviewed Petitioner’s assertions in the Petition concerning claims 11–15, 19, and 20 and Dr. Byrn’s testimony in support, and determine that Petitioner has shown by a preponderance of the evidence that these claims would have been obvious over Chia and Akorn.

E. Remaining Ground

Because we have determined that all challenged claims are unpatentable as obvious over Chia and Akorn, we need not reach the issue of whether these same claims are also unpatentable under Ground 2. Therefore, we do not reach this ground.

III. CONCLUSION¹⁴

For the foregoing reasons, we conclude Petitioner has shown by a

¹⁴ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner’s attention to the April 2019 *Notice*

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preponderance of the evidence that claims 1–7 and 11–20 of the ’145 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Patent Owner’s Motion to Exclude Evidence is *denied*;

FURTHER ORDERED that claims 1–7 and 11–20 of U.S. Patent No. 10,940, 145 B2 have been shown by a preponderance of the evidence to be unpatentable under 35 U.S.C. § 103; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See 37 C.F.R. § 42.8(a)(3), (b)(2).*

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In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1–7, 11–20	103	Chia and Akorn	1–7, 11–20	
1–7, 11–20	103	Wu and Akorn ¹⁵		
Overall Outcome			1–7, 11–20	

¹⁵ Because we find these claims are unpatentable over Chia and Akorn, we do not determine their patentability under this ground.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EYENOVIA, INC.,
Petitioner,

v.

SYDNEXIS, INC.,
Patent Owner.

IPR2022-00415
Patent 10,888,557 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
Administrative Patent Judges.

MITCHELL, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Denying Patent Owner's Motion to Exclude
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

A. Background and Summary

On January 7, 2022, Eyenovia, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting an *inter partes* review of claims 1 through 7 and 11 through 20 (the “challenged claims”) of U.S. Patent No. 10,888,557 B2 (Ex. 1001, “the ’557 patent”). *See* 35 U.S.C. §§ 311–319. On April 18, 2022, Sydnexis, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). On May 17, 2022, Petitioner filed an authorized Reply addressing the public accessibility of Exhibit 1004¹ and Patent Owner’s proposed claim construction for “buffer” and “buffering agent.” *See* Paper 7; Ex. 3001, 3–4. On May 24, 2022, Patent Owner filed an authorized Sur-reply. Paper 8; Ex. 3001.

On July 15, 2022, we granted institution of an *inter partes* review of claims 1–7 and 11–20 of the ’557 patent on all grounds set forth in the Petition. *See* Paper 9 (“Dec.”) 2, 46.

Patent Owner filed a Response on October 21, 2022, *see* Paper 19 (“Resp.”), and Petitioner filed a Reply on January 13, 2023, *see* Paper 21 (“Reply”). Patent Owner filed its Sur-Reply on February 24, 2023. Paper 24 (“Sur-Reply”). An oral hearing was held on April 14, 2023, and a transcript of this hearing was entered into the record. Paper 36 (“Tr.”).

Patent Owner filed a Motion to Exclude Evidence on March 24, 2023. Patent Owner seeks to exclude Exhibit 1002, the Declaration of Dr. Byrn, Petitioner’s declarant, Exs. 1004 and 1057 constituting the Akorn labels, and Exhibits 1079 through 1088, Eyenovia’s Reply exhibits. Paper 29.

¹ Atropine Sulfate Ophthalmic Solution, USP 1%, NDA 206289 Product Label (July 2014) (Ex. 1004, “Akorn”).

Petitioner opposed the motion, *see* Paper 30, and Patent Owner filed a reply, *see* Paper 32. For the reasons set forth herein, the motion is *denied*.

This is a Final Written Decision under 35 U.S.C. § 318(a) as to the patentability of the challenged claims on which we instituted trial. Based on the complete record before us, we determine as set forth below that Petitioner has shown by a preponderance of the evidence that claims 1–7 and 11–20 of the ’557 patent are unpatentable.

B. Real Parties in Interest

Petitioner identifies itself as the real party-in-interest for Petitioner, and states that “Eyenovia, Inc. is not controlled by any other entity.” Pet. 62. Patent Owner identifies itself as the real party-in-interest for Patent Owner. Paper 4, 2; Paper 27, 2.

C. Related Matters

The parties identify that two patents that are related to the ’557 patent, U.S. Patent No. 10,842,787 (“the ’787 patent”) and U.S. Patent No. 10,940,145 (“the ’145 patent”), are the subject of two co-pending requests for *inter partes* review: *Eyenovia, Inc. v. Sydnexis, Inc.*, Case IPR2022-00384 (PTAB) (involving the ’787 patent) and *Eyenovia, Inc. v. Sydnexis, Inc.*, Case IPR2022-00414 (PTAB) (involving the ’145 patent). Pet. 63; Paper 4, 2.

Petitioner also states that the ’557, ’787, and ’145 patents claim dependency to the same application, 14/726,139 (“the ’139 application”), which issued as U.S. Patent No. 9,421,199 (“the ’199 patent”). Pet. 63. Petitioner states:

The ’199 patent was challenged in IPR2021-00439 filed on February 3, 2021 by Nevakar, Inc. who also filed petitions in

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IPR2021-00440 challenging related U.S. Patent No. 9,770,447 on February 17, 2021, IPR2021-00441 challenging related U.S. Patent No. 10,076,515 on March 3, 2021, and IPR2021-00442 challenging related U.S. Patent No. 10,201,534 on March 18, 2021 (collectively, the “Nevakar IPRs”). All of the patents challenged by the Nevakar IPRs also claim the benefit of the ’139 application, and all of the Nevakar IPRs were terminated based on an underlying settlement prior to institution and before any consideration of the cited prior art by the Board.

Pet. 63.

D. The ’557 Patent

The ’557 patent issued on January 12, 2021, and is titled “Ophthalmic Composition.” Ex. 1001, codes (45), (54). The named inventors are Gregory I. Ostrow, Kenneth J. Widder, David S. Baker, and Harun Takruri. *Id.* at code (72). The ’557 patent claims priority to Application No. 16/785,413. See *id.* at code (21).

The subject matter of the ’557 patent involves an ophthalmic composition that includes “a low concentration of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.” Ex. 1001, Abst., 10:57–64. The ’557 patent also provides that the ophthalmic agent may be a muscarinic antagonist, such as atropine or its pharmaceutically acceptable salts, that is known to prevent or arrest the development of myopia in humans. *Id.* at 10:64–65, 9:56–58, 11:7–8. Myopia is characterized by an axial elongation of the eye that begins during grade school years and progresses until growth of the eye is complete. *Id.* at 10:46–49.

The '557 patent describes a balance between having a stabilized ophthalmic composition with an extended shelf life for effective delivery to the patient and avoiding discomfort such as pain or burning sensation in the eye of a patient. *Id.* at 9:47–13. For instance, formulating a liquid muscarinic antagonist composition at a lower pH, such as 4.5, for stability of the composition may cause pain or a burning sensation in the eye of a patient or elicit a tear response reducing the absorption and effectiveness of the atropine. *Id.* at 10:9–16.

The '557 patent also recognizes that using lower concentrations of atropine, e.g. 0.001% to 0.05%, presents stability challenges that are not found in higher concentrations from 0.1 to 1%. *Id.* at 10:17–21. The reasoning for this difference in stability is described as follows.

[T]he concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the pH or pD of the ophthalmic composition, such as with the muscarinic antagonist acting as a buffering agent. Furthermore, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the interaction between the muscarinic antagonist and other ingredients of the ophthalmic composition, which in turn affects the stability of the ophthalmic composition.

Id. at 10:25–33.

The '557 patent further explains that certain embodiments of the invention may further comprise additional agents, including an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, a pH adjusting agent, and a pharmaceutically acceptable carrier. *Id.* at 7:47–8:42.

E. Illustrative Claims

Petitioner challenges claims 1 through 7 and 11 through 20 of the '557 patent. Claim 1, the sole independent claim challenged, is directed to a

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method of treating the progression of myopia or reducing the progression rate of myopia in an individual. *See* Ex. 1001, 100:12–18.

Claim 1 is illustrative of the method and recites:

1. A method of treating progression of myopia or reducing the progression rate of myopia in an individual in need thereof, comprising administering to an eye of the individual (a) an aqueous solution comprising atropine or atropine sulfate and less than about 10% of a degradant of atropine or atropine sulfate formed from degradation of the atropine or atropine sulfate and (b) a buffering agent.

Id. at 100:12–18.

F. Prior Art and Asserted Grounds

Petitioner argues that claims 1 through 7 and 11 through 20 of the '557 patent are unpatentable based on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–7, 11–20	103 ²	Chia, ³ Akorn, ⁴ Kondritzer ⁵

² The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102, 103, and 112, effective March 16, 2013. Because the earliest application on which the '557 patent claims priority was filed after the effective date of the AIA, we apply the AIA version of 35 U.S.C. § 103. *See* Ex. 1001, codes (22), (60), (63).

³ Audrey Chia et al., *Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)*, 119 OPTHALMOLOGY 347–54 (2012) (Ex. 1003, “Chia”).

⁴ Atropine Sulfate Ophthalmic Solution), NDA 206289 Product Label (Revised July 2014) (Ex. 1004, “Akorn”).

⁵ Albert A. Kondritzer & Peter Zvirblis, *Stability of Atropine in Aqueous Solution*, 46 J. AM. PHARM. ASSOC. 531–35 (1957) (Ex. 1005, “Kondritzer”).

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Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–7, 11–20	103	Chia, Akorn, Lund ⁶
1–7, 11–20	103	Akorn, Wu, ⁷ Kondritzer

Petitioner submits the Declaration of Stephen Byrn, Ph.D., in support of its Petition. *See* Ex. 1002 (“the Byrn Declaration”). Patent Owner submits the Declaration of Paul A. Laskar, Ph.D., in support of its Patent Owner Response. *See* Ex. 2003 (“the Laskar Declaration”).

II. ANALYSIS

A. Principles of Law

1. Burden

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016 (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”))). Therefore, in an *inter partes* review, the burden of proof is on the Petitioner to show that the challenged claims are unpatentable, and that burden never shifts to the patentee. *See* 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).

⁶ Walter Lund & Tor Waaler, *The Kinetics of Atropine and Apotrope in Aqueous Solutions*, 22 ACTA CHEM. SCAND. 3085-97 (1968) (Ex. 1007, “Lund”).

⁷ Wu et al., U.S. Patent Pub. No. 2007/0254914, pub. Nov. 1, 2007 (Ex. 1009, “Wu”).

2. Obviousness

To ultimately prevail in its challenge to Patent Owner's claims, Petitioner must demonstrate by a preponderance of the evidence⁸ that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains ("POSA" or "POSITA"). *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In determining obviousness when all elements of a claim are found in various pieces of prior art, "the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success." *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) ("When an obviousness determination relies on the combination

⁸ The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

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of two or more references, there must be some suggestion or motivation to combine the references.”). “Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 1381 (finding a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.”) (internal quotations and citations omitted).

An obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. Section 103 “bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. *KSR*, 550 U.S. at 399 (stating that obviousness is determined against the backdrop of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the art). Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner asserts that “[a] person of ordinary skill in the art (‘POSA’) at the time of the purported invention would have had a Ph.D. in chemistry, organic chemistry, physical chemistry, or pharmaceuticals, with several years of experience preparing and/or testing pharmaceutical formulations.” Pet. 22 (citing Ex. 1002 ¶¶ 61–62). Petitioner further contends that “[a] POSA would have been familiar with common inactive ingredients used in aqueous pharmaceutical formulations and the basic characteristics of aqueous formulations such as stability, and would have had knowledge about drug degradation kinetics.” *Id.*

Patent Owner asserts that a narrower definition of a POSA should be employed—one that includes expertise in ophthalmic formulation.

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PO Resp. 4.⁹ Patent Owner states that Petitioner’s declarant, Dr. Byrn, has “extremely limited experience with ophthalmic formulation,” which “calls into serious question whether he is qualified to opine on the perspective of a POSA in the relevant field.” *Id.* at 5.

We do not agree with Patent Owner that the level of ordinary skill in the art should be limited to experience with ophthalmic formulation. The claims at issue generally recite a method for treating myopia by administering to the eye an aqueous ophthalmic formulation of atropine or atropine sulfate and buffer that has less than 10% of a degradant of atropine or atropine sulfate. *See* Ex. 1001, 100:12–18 (claim 1). As Dr. Byrn points out, the technology surrounding use of atropine, a nonselective muscarinic antagonist, to treat myopia, has been extensively studied for over a hundred years and is known as “the oldest and most effective pharmacological treatment to inhibit the development of myopia.” *See* Ex. 1002 ¶ 26 (quoting Ex. 1008, 1) (citing Ex. 1003, 1; Ex. 1012, 2). The degradation of atropine is also well known to primarily result from cleavage of the acyl-oxygen bond during ester hydrolysis, *see id.* ¶ 43 (citing Ex. 1017, 1; Ex. 1024, 5), with the rate of acid-catalyzed reaction being much slower than that of the base-catalyzed reaction, leading to stability of atropine at a lower pH range (pH < ~3), *see id.* ¶ 45 (citing Ex. 1005, 1, 4–5). Concerning specifically the use of atropine in the eye, Dr. Byrn points out that it is well known that ophthalmic solutions should be “formulated to be sterile, isotonic and buffered for stability and comfort.” *See* Ex. 1002 ¶ 47 (quoting Ex. 1019, 52) (noting Ex. 1019, 54 (pH of tear fluid is 7.4).

⁹ Although Patent Owner disagrees with Petitioner’s definition of a POSA, Patent Owner does not provide its own definition apart from including expertise in ophthalmic formulation. *See* PO Resp. 4–7.

None of this chemistry concerning the stability of atropine or its administration in the eye is remarkable or not well understood by a POSA as defined by Petitioner. *See* PO Resp. 10 (stating “the stability of atropine was understood to be a ‘predictable function,’ and a ‘routine matter,’ of temperature and solution pH”), 41–42 (same). We see no reason why someone with drug formulation experience, but not specific experience with ophthalmic solutions, would not qualify as a POSA. Therefore, we continue to apply Petitioner’s definition of a POSA in this final written decision.

C. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 100(b) (2019). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioner states that “[f]or the purposes of this proceeding only, Petitioner does not believe that any claim terms need to be construed.” Pet. 22. Patent Owner “agrees that the claims should be understood according to their ordinary and customary meaning.” PO Resp. 25. In reply, Petitioner asserts that the ordinary meaning of “about” is “approximately,”

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and the ordinary meaning of “buffering agent” or “buffer” “is nothing more than an excipient that helps control pH.” Reply 2. Petitioner asserts that Patent Owner agrees with the definition of “buffering agent” and “buffer” by stating that “[t]he patent uses terms buffer and buffering in their normal sense, which entails providing pH control or maintenance.” *Id.* (quoting PO Resp. 29).

Based upon our review of the evidence of record, we determine that no claim terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (Only those terms that are in controversy need be construed, “and only to the extent necessary to resolve the controversy.”). Insofar as the parties dispute whether Akorn discloses a buffer, we address those contentions in our discussion below of the challenged claims.

D. Obviousness over Chia, Akorn, and Kondritzer

Petitioner asserts that claims 1 through 7 and 11 through 20 would have been obvious over the combined teachings of Chia, Akorn, and Kondritzer. Pet. 23–42. In addition to challenging the public availability of Akorn, Patent Owner disagrees and states that the Akorn reference “does not disclose the phosphate salts are buffering agents. Nor does it disclose that the Akorn product has a pH range of 3.5–6.0. Each of these failures is case-dispositive.” PO Resp. 1.

1. Chia (Ex. 1003)

Chia is a journal article that describes two studies regarding the treatment of myopia using atropine eyedrops. Ex. 1003, 1. In the first study, Atropine for the Treatment of Myopia 1 (“ATOM1”), it was shown that atropine 1% eyedrops were effective in controlling myopic progression but

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with visual side effects resulting from cycloplegia and mydriasis. *Id.* The second study described in Chia, Atropine for the Treatment of Myopia 2 (“ATOM2”), compared the efficacy and visual side effects of 3 lower doses of atropine: 0.5%, 0.1%, and 0.01%. *Id.* The authors of Chia conclude “[a]tropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression.” *Id.*

Chia notes that atropine, a nonspecific muscarinic antagonist, at 1.0% and 0.5% has been shown to be effective in slowing myopia progression, but its safety profile regarding pupil size and accommodation was a concern.

Ex. 1003, 6. Chia states:

Every unit increase in pupil size results in an exponential increase in the amount of light entering the eye, and this can cause glare and potential phototoxicity. Atropine also decreases accommodation amplitude and near vision so that children may require bifocal or progressive glasses to read. The ideal atropine dose would be one with the best balance between efficacy and safety.

Id.

To explore the ideal atropine dose, Chia performed the ATOM2 study using 0.01% atropine as a potential control due to its assumed minimal effect. Ex. 1003, 7. Chia found that “contrary to expectations, atropine 0.01% also had significant clinical effects as evidence by its effect on myopia progression, accommodation, and pupil size.” *Id.* In comparing the 0.01% atropine dose to the 0.5% and the 0.1% doses, Chia found “the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared with the 0.5% group. Likewise, the difference in axial length increase was statistically larger than in both the 0.1% and 0.5% groups. However, absolute differences between groups were

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clinically small” *Id.* Chia did note that no other atropine 0.01% studies were available for direct comparison, but Chia did compare the data to a study¹⁰ testing 0.05% atropine and a study¹¹ testing 0.025% atropine. *Id.*

Although Chia found that “[o]verall, atropine-related adverse effects were uncommon at the 0.01% dose . . . [t]here are no long-term studies on the effect of atropine on the eye, and continued vigilance is necessary. However, atropine has been clinically available since the early 1900s, and so far there are no known long-term adverse effects associated with its use.” Ex. 1003, 7. Chia states:

In conclusion, our results suggest that 0.5%, 0.1%, and 0.01% atropine remain effective in reducing myopia progression, compared with placebo treatment, and that the clinical differences in myopia progression among these 3 groups are small. The lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while attaining a clinically significant improved safety profile in terms of accommodation, pupil size, and near visual acuity, and subsequently reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer adverse events. Atropine 0.01% is currently not commercially available. However, these findings collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.

Id. at 7–8.

¹⁰ Lee et al., *Prevention of myopia progression with 0.05% atropine solution*, 22 J. OCUL. PHARACOL. THER. 41–46 (2006) (Ex. 1012, “Lee”).

¹¹ Fang et al., *Prevention of myopia onset with 0.025% atropine in premyopic children*, 26 J. OCUL. PHARMACOL. THER. 341–345 (2010) (Ex. 1013, “Fang”).

2. *Akorn (Ex. 1004)*

Petitioner identifies Ex. 1004 as a product label for Akorn Atropine Care, which appears to be an excerpt from New Drug Application 206289. *See* Pet. vii; Ex. 1004, 1. Akorn describes a 1% atropine sulfate ophthalmic solution for topical application to the eye. Ex. 1004, 1. Akorn explains that atropine is an anti-muscarinic agent that is indicated for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia. *Id.* at 1, 2. Akorn explains atropine's mechanism of action as follows:

The pupillary constrictor muscle depends on muscarinic cholinergic activation. This activation is blocked by topical atropine resulting in unopposed sympathetic dilator activity and mydriasis. Atropine also weakens the contraction of the ciliary muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate such that the eye cannot focus for near vision.

Id. at 4. Akorn describes applying 1 drop of the solution to the cul-de-sac of the conjunctiva forty minutes prior to an intended maximum dilation time. *Id.*

Akorn explains that the solution contains atropine sulfate as an active ingredient. *Id.* at 3. Akorn further describes the following inactive ingredients: “benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.” *Id.*

3. *Kondritzer (Ex. 1005)*

Kondritzer is a journal article that relates to a kinetic study of the proton catalyzed hydrolysis of atropine “to identify and evaluate the factors involved in the deterioration of aqueous solutions of atropine and its salts,” and confirmed the temperature dependency of the reaction. Ex. 1005, 1.

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Kondritzer explains that the alkaline hydrolysis of atropine in aqueous solution involves two reactions: “one involving the unprotonated (base) form, and the other the protonated (ionic) form of the alkaloid,” with each reaction being governed by hydroxyl-concentration and temperature. *Id.* Kondritzer also notes some previous work concerning the stability of aqueous atropine solutions stating: “The preservation of aqueous atropine solutions by buffering at pH 4–5 has been recommended.” *Id.* at 2.

Kondritzer’s evaluation included studying the hydrolysis of atropine in various perchloric acid solutions at temperatures varying from 70° C to 90° C. *Id.* at 2. Based on this, Kondritzer prepared an equation to predict the rate of proton hydrolysis at any particular temperature and hydrogen ion concentration. *Id.* Kondritzer takes into account the effect of both hydroxyl and hydrogen ions to determine the pH of minimum hydrolysis at various temperatures and calculates the hydrolytic rates at these minimum pH values. *Id.* Kondritzer also calculates the half lives of atropine solutions for various pH values and temperatures. *Id.*

From measuring the rate of acid hydrolysis of atropine in aqueous solution, Kondritzer concludes that the predominant catalytic reaction above pH 4.5 involves the hydroxyl ion, and the predominant catalytic reaction below pH 3 involves the hydrogen ion. *Id.* at 4. Kondritzer also states:

The half lives of solutions of atropine at various pH values and temperatures can be calculated for both hydroxyl-ion and hydrogen-ion catalysis. The former accounts for the instability above approximately pH 5 and the latter for instability below approximately pH 3. The half life at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical.

Id.

Kondritzer states that “[a]s expected, the hydrogen ion catalyzed hydrolysis of atropine is slow.” *Id.* Based on the study, Kondritzer concludes that “[t]he pH for maximum stability of atropine in sterile aqueous solution varies between 4.11 at 0° and 3.24 at 100°.” *Id.* at 5.

4. *Analysis*

For its assertion that claims 1–7 and 11–20 would have been obvious over the combined teachings of Chia, Akorn, and Kondritzer, Petitioner relies on Akorn as teaching or suggesting adding to Chia’s low concentration atropine solutions for treating myopia progression a buffering agent to achieve a pH range of 3.5 to 6.0 to stabilize Chia’s low concentration atropine solutions and minimize the formation of degradants while maintaining clinical efficacy. Pet. 23–32. Patent Owner challenges Petitioner’s reliance on Akorn asserting that the Petition fails to prove that Akorn was publicly available prior to the undisputed critical date of April 23, 2015, which Patent Owner also raised in its Preliminary Response. *See* PO Resp. 58–61; Prelim. Resp. 30. Patent Owner also challenges the testimony of Dr. Byrn in its Motion to Exclude Evidence asserting that “Dr. Byrn’s proffered opinions exceed his expertise, are not based on ‘scientific knowledge,’ ‘sufficient facts or data,’ and are not ‘the product of reliable principles’ and methods ‘reliably applied’ to the facts of this case.” Paper 29, 2 (“Mot. to Exclude”).

Because the prior art status of Akorn and Dr. Byrn’s testimony is relevant to all grounds asserted by Petitioner, we begin our discussion with these issues.

a) Prior Art Status of Akorn (Ex. 1004)

Petitioner has the burden to prove Akorn qualifies as prior art. *See In re Magnum Oil Tools*, 829 F.3d at 1376. “[A]t the institution stage, the petition must identify, with particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication.” *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 (“Hulu”) at 13 (PTAB Dec. 20, 2019) (precedential).

“[P]ublic accessibility” is considered to be “the touchstone in determining whether a reference constitutes a ‘printed publication’ bar under 35 U.S.C. §102(b).” *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). “A given reference is ‘publicly accessible’ upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.” *SRI Int’l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

A determination whether a particular reference qualifies as a printed publication “is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis.” *Hall*, 781 F.2d at 899. In a proceeding before the Board, there is no presumption in favor of finding that a reference is a printed publication. *Hulu*, Paper 29 at 16.

During the institution phase of this proceeding, we authorized further briefing on the issue of whether Akorn was publicly accessible before the critical date, and each party filed a brief addressing this issue. *See* Ex. 3001; Paper 7; Paper 8. In our Institution Decision, we addressed the parties’

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arguments and determined on the record before us at that time that “Petitioner has adequately shown for institution that Akorn was sufficiently accessible to the public interested in the art and searchable on the DailyMed website such that a POSA could have found it with reasonable diligence.” Dec. 33. In making this determination, we examined Petitioner’s additional evidence, Exhibit 1057, that it submitted with its reply to the preliminary response, and determined “that Petitioner properly relies on Exhibit 1057 as additional evidence to confirm that Exhibit 1004 was published and publicly accessible in July of 2014.” *See* Dec. 33.

In making this determination, we made the following findings concerning Exhibit 1057 for purposes of institution.

In particular, on the current record, we find that Petitioner’s Exhibit 1057 provides persuasive corroboration for its contention that Akorn was publicly accessible in July of 2014. Exhibit 1057 includes printouts of webpages from “DailyMed.” Ex. 1057. In the “ABOUT DAILYMED” section on the first page of the exhibit, there is a statement explaining that “The National Library of Medicine (NLM)’s DailyMed searchable database provides the most recent labeling submitted to the Food and Drug Administration (FDA) by companies and currently in use (i.e., ‘in use’ labeling).” *Id.* at 1. Among other items, the DailyMed “contains labeling for prescription and nonprescription drugs for human and animal use.” *Id.* The statement also explains that “[t]he NLM provides DailyMed to the public” and “[t]he labeling on DailyMed is typically reformatted to make them easier to read.” *Id.*

On the third page of Exhibit 1057, there is a copy of the DailyMed “LABELING ARCHIVES” webpage which depicts a “Labeling Archives Search,” with a first field for entering a drug name, and a second field for entering a date. *Id.* at 3. The webpage explains that “[t]his archive allows the user to retrieve the label current for a given date.” *Id.* Search results for the term “ATROPINE SULFATE” on “07/31/2014” are displayed. *Id.* There is an indication that the search provided 135 results which

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are listed in a row, apparently over a number of webpages. *Id.* The results are organized with the “DATE POSTED” identified in one column, along with the term “download” which appears to be formatted as a web link, and the “DRUG NAME” identified in a second column, wherein the drug name listed appears to be formatted as a web link. *Id.* Below the drug name, the name of the “Packager” is identified, along with a “Version” number. *Id.* Petitioner draws our attention to the label identified with July 24, 2014, as the “DATE POSTED,” “Atropine (atropine sulfate) solution/drops,” as the “DRUG NAME,” Akorn, Inc. as the “Packager,” with the “Version” noted as “7.” *Id.*

We understand the next page of the exhibit to be a copy of the DailyMed webpage depicting the version 7 label for Akorn’s atropine sulfate that was posted on July 24, 2014. Ex. 1057, 4. Based on our review, but for minor web-related formatting differences, this label posted on DailyMed appears to be the same as the label depicted in Exhibit 1004. In particular, we observe that both labels: (a) refer to “HIGHLIGHTS OF PRESCRIBING INFORMATION” for “Atropine Sulfate Ophthalmic Solution, USP 1% for topical application to the eye;” (b) include the “Revised: 7/2014” statement; (c) include the same indications and usage, dosage and administration; (d) set forth the same sections/subsections; and (e) describe the contents of the drug in the same manner, including the statement identifying inactives as: “benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.” *Compare* Ex. 1004, 1–5, *with* Ex. 1057, 4–6.

Taken together, we find that the evidence relied on in the Petition, i.e., Exhibits 1004, 1020, 1021, along with Exhibits 1056, 1058, and especially, 1057, submitted with the Reply, provide strong indicia that the July 2014 version of Akorn’s atropine sulfate drug label represented on the current record as Exhibit 1004 was posted on July 24, 2014, on the DailyMed website. We do not find any dispute on the current record that DailyMed is a federal government website that is accessible to the public and presented in a manner that allows the public to readily search its database for drug labels that have been

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approved by the FDA. Moreover, as Petitioner asserts, the DailyMed website explains, “The DailyMed RSS feed provides updates and information about new drug labels approved by the FDA and published on NLM’s DailyMed Web site.” Ex. 1057, 1. In other words, the DailyMed website further extends its reach to the public through such feed.

Dec. 30–32.

Patent Owner in its Response continues to question the public availability of Akorn. *See* PO Resp. 58–60. Patent Owner continues to assail the public availability of Akorn as shown by the exhibits originally presented with the Petition, *see id.* at 58–60, but we agreed with some of these criticisms. For instance, we stated:

To begin, we note that, in some respects, we agree with Patent Owner’s position. For example, we agree with Patent Owner that the “7/14” revision date printed on Akorn, on its own, indicates only that some unknown author(s) modified the document on that date. *See* Prelim. Resp.30, PO Sur-reply 2–3. Indeed, similar to the copyright or creation dates in *Hulu*, the revision date, by itself, is insufficient to demonstrate that the exhibit was publicly available on that date. *See Hulu*, Paper 29 at 19. We also agree with Patent Owner that neither the FDA approval date of the Akorn atropine sulfate drug product nor the sale or use of that product demonstrates the public accessibility of drug label reflected in Akorn prior to the critical date. *See* Prelim. Resp. 30–31, Sur-reply 2–3.

Dec. 29. Our decision on the public availability of Akorn turned on the additional evidence Petitioner submitted as Exhibit 1057. *See id.* at 30–35.

The only criticism Patent Owner presents with reference to our analysis of Exhibit 1057 as set forth above is to question a statement on the DailyMed webpage concerning when filtering by published date was added to Web Services. *See* PO Resp. 60; Sur-Reply 24–25. Patent Owner states: “But Petitioner’s DailyMed exhibit (created on September 15, 2021) acknowledges that “Filtering by Published Date [Was] Added to Web

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Services” only as late as October 2015 (EX1057, 1, 2), which falls after the critical date. EX1001, Cover. As the very same search means that Petitioner used to find the label in EX1057 admittedly did not exist before the critical date, Petitioner has failed to demonstrate pre-critical date public availability of this new label.” PO Resp. 60.

We find that Patent Owner’s criticism misses the mark. Petitioner is using the DailyMed exhibit as further evidence that Akorn was publicly available as of the revision date of 7/2014 as shown on Akorn, Ex. 1004. *See* Opp. Mot. to Exclude 8 (stating “public records from DailyMed, part of the NIH’s National Library of Medicine, show that EX1004 was posted publicly on that site at least by July 24, 2014. *See* EX1057, 3.”). Whether a POSA could have searched this way for labels published before the critical date is irrelevant; Petitioner is only using the evidence to show that Akorn was, in fact, published in July 2014, before the critical date on a searchable website. *See id.* Patent Owner does not dispute that DailyMed was searchable by drug name, which would be the logical way a POSA would search such a database for information for a drug of interest.

Petitioner also provides further evidence that the Akorn label was published on July 24, 2014, through a response by the National Library of Medicine (“NLM”) to a Freedom of Information Act request. *See* Ex. 1071. In this Freedom of Information Act request, Petitioner asked for written confirmation that the substance of the Akorn label was posted on July 24, 2014 on the DailyMed website. *Id.* The National Institutes of Health (“NIH”) responded that version 7 of the Akorn label was published on DailyMed on July 24, 2014, and provided the URL that is reflected in the Akorn label in Exhibit 1057 from the DailyMed website. *See* Ex. 1072, 6; Ex. 1057, 4–7. NIH also confirmed that NLM “received version 7 of this

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label from the FDA on 07/24/2014 @ 2:15:04 PM,” “published version 7 on DailyMed on the same day, 07/24/2014 @ 14:59:48 PM,” and confirmed that “NLM does not make changes to the content contained within any SPL [or structured product labeling] records that it receives from the FDA.”

Ex. 1072, 6. We find that Petitioner has provided more than sufficient evidence that the Akorn label reflected in Ex. 1004 was publicly available before the critical date.

For the reasons set forth above, we determine that Petitioner has shown by a preponderance of the evidence that Akorn, Ex. 1004, is a printed publication that was publicly available before the critical date.

b) Patent Owner’s Motion to Exclude Evidence

Patent Owner moves to exclude from evidence the Declaration of Dr. Byrn (Ex. 1002), Exhibits 1004 and 1057 that constitute the Akorn labels, and Exhibits 1079 through 1088 that Petitioner submitted with its Reply. Mot. to Exclude 2. Petitioner filed an Opposition (Paper 30, “Opp. to Mot. to Exclude”), and Patent Owner filed a Reply (Paper 32, “Reply to Mot. to Exclude”). For the following reasons, Patent Owner’s Motion to Exclude is *denied*.

Pursuant to our Rules, a motion to exclude evidence must be filed to preserve any previously-made objections to evidence. 37 C.F.R. § 42.64(c). The motion must identify where in the record the objections were made, and must explain the objections. *Id.* Patent Owner appropriately identifies where in the record it previously served objections to the exhibits it seeks to exclude. Mot. to Exclude 2 (citing Papers 12, 22).

As the moving party, Patent Owner bears the burden of proof to establish that it is entitled to the requested relief, i.e., the exclusion of

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evidence as inadmissible under the Federal Rules of Evidence (“FRE”). *See* 37 C.F.R. §§ 42.20(c), 42.64(a).

(1) Dr. Byrn’s Testimony (Ex. 1002)

Patent Owner challenges Dr. Byrn’s testimony under FRE 702 as not based on sufficient “scientific knowledge,” not based on “sufficient facts or data,” and not “the product of reliable principles” and methods “reliably applied” to the facts of this proceeding. Mot. to Exclude 2.

(a) Requisite Scientific Knowledge

For instance, although Dr. Byrn agrees that the ’557 patent is “directed to the field of ophthalmic compositions and ophthalmic solutions,” Patent Owner asserts that Dr. Byrn’s curriculum vitae (Ex. 1002, Appendix A) “provides no indication that Dr. Byrn has any expertise in ophthalmic formulation.” Mot. to Exclude 2–3 (citing Ex. 2009, 97:19–98:14; 104:20–106:5). Patent Owner further states:

During his deposition, Dr. Byrn identified brief eyedrop forays (none significant enough to merit mention in his CV or declaration), but could not identify any ophthalmic product he formulated before the critical date. Even as of 2021, Dr. Byrn never had primary responsibility for formulating any drug product that has received regulatory approval or been commercialized.

Mot. to Exclude 3 (citing Ex. 2010 ¶ 8). Patent Owner also criticized Dr. Byrn’s alleged lack of knowledge of ophthalmic terms such as lacrimation. *See id.*

Petitioner responds that the primary focus in evaluating the admissibility of testimony under FRE 702 is “whether an expert’s opinion will assist the trier of fact,” a low bar, and many of Patent Owner’s criticisms go to the weight to be accorded Dr. Byrn’s testimony rather than

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its admissibility. Opp. to Mot. to Exclude 1–6. In applying FRE 702, Petitioner asserts that “Dr. Byrn, a professor of medicinal chemistry who specializes in drug formulation, is eminently qualified to opine about the straightforward formulation issues presented in this proceeding.” *Id.* at 1.

Petitioner asserts that Patent Owner does not contest that Dr. Byrn meets Petitioner’s POSA definition (as we have determined should be applied in this proceeding), but even if we required experience in formulating ophthalmic pharmaceuticals, we find that Dr. Byrn has such experience. *See* Opp. to Mot. to Exclude 2–4; Ex. 1002, Appendix A ¶¶ 3–10. Petitioner asserts that Dr. Byrn testifies:

That he worked as a consultant for Alcon—a well-known eye care company—on a number of ophthalmic products, including ones that were FDA-approved, prior to the critical date. *See* Ex. 2009, 136:12–137:12. He further testified that he worked with eye drops as part of Purdue’s Africa program. *Id.* at 49:149–50:2.

Opp. to Mot. to Exclude 4. Petitioner also asserts that Dr. Byrn accurately described the term “lacrimation” in his deposition. *Id.* at 4 n.2 (citing Ex. 2009, 49:11–14; Ex. 1002 ¶ 77 (quoting Ex. 1047, 2)).

As we have previously determined, a POSA need not have specific experience in ophthalmic formulation. *See* Section II.B. Dr. Byrn has ample experience to qualify as a POSA, which we defined as a person having a Ph.D. in chemistry, organic chemistry, physical chemistry, or pharmaceuticals, with several years of experience preparing and/or testing pharmaceutical formulations at the time of the purported invention. *See* Section II.B.; Ex. 1002 ¶¶ 3–10. Dr. Byrn has the requisite academic background, as well as extensive experience in drug development and formulation. *See* Ex. 1002 ¶¶ 3–10. Dr. Byrn testifies that his “laboratory

has done extensive research on drug formulations, and [he has] authored over two hundred book chapters and peer-reviewed journal articles on properties of a wide variety of pharmaceutical compositions.” *Id.* ¶ 10.

We also find, however, that Dr. Byrn has experience with ophthalmic formulations. Dr. Byrn testifies that he has “worked quite a bit with eyedrops” in Purdue’s Africa program. Ex. 2009, 49:21–24. In his Declaration, Dr. Byrn testifies that he was a co-founder of the Sustainable Medicines in Africa in the Kilimanjaro and Arusha regions of Tanzania in 2007. Ex. 1002 ¶ 5. Dr. Byrn describes this program more extensively in his curriculum vitae as providing educational programs that are “aimed at providing source of well-trained manufacturing scientists for pharmaceutical industry in Tanzania and Africa,” and including a GMP-level pharmaceutical manufacturing facility to teach manufacturing under strict quality control, as well as a quality medicines laboratory equipped with HPLCs. Ex. 1002, Appendix, 101. Dr. Byrn also testifies that he consulted with Alcon on a number of ophthalmic drug products although he was not primarily responsible for their formulation. *See* Ex. 2009, 136:12–20.

We find Dr. Byrn’s alleged lack of “primary” responsibility for the formulation of an ophthalmic product to be somewhat of a red herring in assessing whether Dr. Byrn has “expertise in ophthalmic formulation” as Patent Owner asserts should be required. *See* Mot. to Exclude 2–3. In response to questions about whether Dr. Byrn ever had primary responsibility for formulating a drug product that has received regulatory approval, Dr. Byrn testifies that he has “been on a team that formulated drug products for both for commercial sale and IND testing.” Ex. 2009, 134:19–24. Dr. Byrn also pointed out what he considered to be a false premise in

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the questions related to “primary” responsibility for drug formulation.

Dr. Byrn testifies:

I have been a consultant on a large number of products that came on the market and I worked in a team, and my work was – part of the work was critical for certain specifications and certain marketing steps, but I don’t believe that in this day and age a person is primarily responsible for bringing a drug on the market; it’s a team activity.

Id. at 135:15–23. We credit Dr. Byrn’s testimony here.¹² We also determine that Dr. Byrn satisfies the requirements for a POSA as we have determined it should be defined, without specific expertise in ophthalmic formulation, but also determine that even if we applied Patent Owner’s heightened standard requiring such expertise, Dr. Byrn satisfies that definition also. Dr. Byrn has the requisite scientific knowledge to serve as an expert for Petitioner.

(b) Sufficiency of Underlying Facts and Data; Reliability of Principles and Methods as Applied to Underlying Facts and Data

Patent Owner asserts that Dr. Byrn’s alleged inexperience with ophthalmic formulations led him to offer an opinion not based on sufficient facts or data or reliable principles, i.e., that Dr. Byrn’s opinion that “Akorn teaches the uses of buffering agents to achieve a solution pH range of 3.5 to 6.0 were ‘premised’ on an undisclosed assumption that the buffering range of the weak acid extends ± 2 pH units away from its pK_a .” Mot. to Exclude 4

¹² We also find that Dr. Byrn was clearly familiar with the term “lacrimation,” which means “the secretion of tears especially when abnormal or excessive,” but chose to use the word “tearing” instead. See Ex. 2009, 49:3–14; see also <https://www.merriam-webster.com/dictionary/lacrimation> (accessed June 25, 2023) (defining lacrimation).

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(citing PO Resp. 37–38; Ex. 2009, 96:5–97:4; Ex. 1002 ¶¶ 20, 24, 53, 65–66, 80, 95, 138, 156–157, 188, 192, 203, 211; Ex. 1040, 23 (Table 8)).

Patent Owner also asserts Dr. Byrn’s assumption has been shown to be incorrect in a district court proceeding in which he testified. *See* Mot. to Exclude 4–7.

Petitioner counters that Dr. Byrn’s opinions are based on sufficient facts and data and are reliable. *Opp. to Mot. to Exclude* 5–6. As an example, Petitioner points to Dr. Byrn’s reliance on Remington (Ex. 1019), which Dr. Laskar admits is a formulator’s “bible,” to establish that “Remington means exactly what it says: buffer capacity represents a compromise between stability and comfort, and thus a buffer with diminished capacity (*e.g.*, the one provided by sodium phosphate salts) should be used.” *Opp. to Mot. to Exclude* 5 (citing Ex. 2003 ¶¶ 62–63; Ex. 1002 ¶ 136).

Petitioner also points to support for Dr. Byrn’s opinion that sodium phosphate salts “can still buffer outside of ± 1 unit away from their pK_a ” in the “reliable scientific literature that Patent Owner seeks to preclude the Board from considering.” *Id.* at 6 (citing Exs. 1079–1083 (buffer recipes using the claimed sodium phosphate salts below pH 6.0)). Finally, Petitioner asserts that Dr. Byrn’s testimony in the district court proceeding is inapposite because

The primary legal issue in that case dealt with infringement under the doctrine of equivalents, and whether a generic company’s “proposed product contains an equivalent to the ‘buffer’ of the claims[.]” *See* Ex. 2010, 2. Unlike here, the alternative excipient that the generic company contended was a buffer had not be identified, disclosed, and claimed as such by the patentee. *See* Ex. 1001 (claim 5).

Opp. to Mot. to Exclude 6–7.

We agree with Petitioner here that Patent Owner's concerns about the sufficiency of the support for Dr. Byrn's opinions goes more to the weight to be accorded such opinions rather than a need to exclude such opinions. *See* TPG 40–41, 79 (“A motion to exclude must explain why the evidence is not admissible (e.g., relevance or hearsay) but may not be used to challenge the sufficiency of the evidence to prove a particular fact.”). We also note that the findings in the district court litigation are based on a different record that is not before us here. For instance, the district court relies on a Lewis reference and a Harris reference that is not before us and testimony from Dr. Richard Moreton that is also not before us here. *See* Ex. 2010 ¶¶ 63–69. Therefore, we determine that the district court's findings are not sufficiently probative of the questions before us here.

Also, the district court's findings are not as definitive as Patent Owner states. The patent owner in the district court case attempted to prove infringement by the doctrine of equivalents for a formulation that did not expressly contain a buffer, but that it argued inherently contained a buffer from the chemical disassociation of the active ingredient in the product. *See* Ex. 2010, 64–65. The district court found that patent owner failed to prove that this actually occurs in the accused product. *Id.* at 65. The district court case is in stark contrast with the underlying facts of this proceeding in which the prior art formulation expressly contains the same buffers as claimed in the '557 patent. *See* Ex. 1001, 100:34–36 (claim 5); Ex. 1004, 3.

(c) Conclusion

Based on the foregoing, we *deny* Patent Owner's motion to exclude Exhibit 1002, Dr. Byrn's testimony.

(2) The Akorn Labels (Exs. 1004 and 1057)

Patent Owner asserts that Exhibits 1004 and 1057 should be excluded because Petitioner failed to show that Exhibit 1004 (Akorn) was publicly available before the critical date, and Exhibit 1057 is deficient to show such public availability of Exhibit 1004. Mot. to Exclude 7–8.

We have previously addressed these issues in our determination of the prior art status of Akorn, Ex. 1004, set forth above. *See* Section II.D.4.a). For these same reasons, we *deny* Patent Owner’s motion to exclude Exhibits 1004 and 1057.

(3) Exhibits 1079–1088

Patent Owner moves to exclude Exhibits 1079 through 1088 submitted with Petitioner’s Reply. *See* Mot. to Exclude 2, 8–15. Patent Owner asserts that these exhibits should have been submitted with the Petition and are untimely. *Id.* at 8. Patent Owner also asserts that Dr. Byrn did not “elect to submit a Reply declaration, rely upon any of these documents, or testify that any of them are the kinds of documents an expert in his field (much less a POSA in the field of the invention) would rely upon.” *Id.*

Petitioner asserts that these documents were presented to Dr. Laskar at his deposition to rebut Patent Owner’s assertions that “two common buffering agents, sodium dihydrogen phosphate and disodium hydrogen phosphate—identified and claimed by the ’557 patent as buffering agents—are not buffers in the claimed range of about 4.8 to about 6.4.” Opp. to Mot. to Exclude 10 (citing PO Resp. 35; Ex. 2003 ¶ 56).

Our Trial Practice Guide states that:

Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima

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facie case of unpatentability. A party may also submit rebuttal evidence in support of its reply.

Patent Trial and Appeal Board Consolidated Trial Practice Guide 73 (Nov. 2019) (citing *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1077–78 (Fed. Cir. 2015)).

Here, we find that Exhibits 1079 through 1088 are appropriate rebuttal evidence. Petitioner uses these exhibits to test Dr. Laskar’s opinions concerning the buffering range for sodium dihydrogen phosphate and disodium hydrogen phosphate. *See generally* Ex. 1078, 91–189.¹³ As the Federal Circuit noted in *Belden*, there is no bright-line demarcation between support for Petitioner’s prima facie case and rebuttal evidence. For instance, the Federal Circuit stated that using rebuttal evidence as support for the prima facie case does not necessarily mean that it was “necessary” for the prima facie case requiring it to be in the Petition.

Evidence admitted in rebuttal to respond to the patent owner’s criticisms will commonly confirm the prima facie case. That does not make it necessary to the prima facie case. And nothing required the Board to write its opinion to separate the material offered by [petitioner] at different stages of the proceeding.

See Belden, 805 F.3d at 1079.

For these reasons, we *deny* Patent Owner’s motion to exclude Exhibits 1079 through 1088.

¹³ In response to Patent Owner’s Objections to Evidence, Petitioner also provided a Declaration of Rebecca L. Baker, a Research Analyst at the law firm representing Petitioner, attesting to the authenticity of Exhibits 1079, 1081–1085. *See* Ex. 1095.

c) Claim 1

Petitioner asserts that claim 1 recites elements previously known in Chia and Akorn: “(1) the use of atropine and low-concentration atropine solutions to treat myopia progression as taught by Chia, combined with (2) well-known buffering agents to achieve a pH range known to prevent degradation of the atropine solution while maintaining clinical efficacy.” Pet. 23. The claimed “stabilized” atropine solution of claim 1 requiring no more than 10% of an atropine “degradant” is formed, Petitioner asserts, is an expected result of the combination of Chia’s low-concentration atropine formulation and Akorn’s buffering agents. *Id.*

Petitioner describes what it terms the “ample” motivation to make such a combination and the reasonable expectation of success for such a combination as follows. *See* Pet. 23–24 (citing Ex. 1002 ¶¶ 64–78).

In 2012, *Chia* disclosed that atropine, and specifically low-concentration atropine, eye drops effectively treated myopia and reduced patient compliance issues associated with higher concentration compositions. Ex. 1003, 7–8. Because atropine’s pH-dependent stability was well known in the art, a POSA would have looked to FDA-approved atropine ophthalmic solutions for a suitable buffering system to prevent degradation of the solution. Ex. ¶ 65. Thus, a POSA would have been motivated to use *Akorn*’s buffers and pH range of 3.5–6.0 for the atropine solution disclosed in *Chia*. A POSA would have confirmed that this pH range was appropriate via routine experimentation and based on the predicted stability of atropine at various pHs disclosed in *Kondritzer*.

Pet. 23–24.

Patent Owner responds that Akorn “does not disclose the phosphate salts are buffering agents. Nor does it disclose that the Akorn product has a pH range of 3.5–6.0. Each of these failures is case dispositive,” as all grounds rely exclusively on Akorn “to disclose a stabilized atropine

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ophthalmic aqueous solution comprising a buffering agent such that no more than 10% of an atropine degradant is formed.” PO Resp. 1, 25–26. Patent Owner also asserts that Petitioner’s only motivation for making the claimed combinations in the ’557 patent results from improper hindsight. *See* PO Resp. 41–50.

(1) Uncontested Limitations

We begin our analysis with the limitations of claim 1 that Patent Owner does not dispute are taught by the prior art. Petitioner points to both Chia and Akorn as teaching the preamble “[a] method of treating progression of myopia or reducing the progression rate of myopia in an individual in need thereof.” Pet. 29–30; *see* Ex. 1002 ¶¶ 83–85. Chia describes the ATOM2 study, which “examined the effect of lower doses of atropine to determine whether these concentrations could result in efficacy in preventing myopia progression, with less visual side effects (i.e., pupil dilation, loss of accommodation, and near vision blur).” Ex. 1003, 1–2. Petitioner points out that Chia also discloses that the study participants had “myopic refraction of at least 2.0 D in both eyes” and “documented myopic progression of at least 0.5 D in the past year.” Pet. 29 (quoting Ex. 1003, 2; Ex. 1002 ¶ 84). Because those participants were administered doses of atropine sulfate eye drop solution “once nightly in both eyes,” Petitioner asserts “*Chia* renders obvious claim 1’s ‘method of treating progression of myopia or reducing the progression rate of myopia in an individual in need thereof.’” Pet. 29; Ex. 1002 ¶ 84.

Petitioner also relies on Akorn for teaching the preamble by disclosing an FDA-approved, commercially available atropine sulfate ophthalmic solution that has buffering agents. Pet. 29. Dr. Byrn testifies that “atropine

has been used to treat myopia for decades,” therefore, “[i]n view of the common knowledge regarding this use of atropine, and in view of *Chia*, administering *Akorn*’s atropine sulfate ophthalmic solution to treat myopia would have been obvious.” Ex. 1002 ¶ 85.

We agree with Petitioner that *Chia* teaches a method for treating or reducing the progression of myopia in an individual in need as described in the ATOM2 study. We also agree with Dr. Byrn’s assessment of a POSA using a commercially available, FDA-approved atropine product, such as *Akorn*, to treat myopia would have been obvious.

Petitioner asserts that the combination of *Chia*, *Akorn*, and *Kondritzer* teach the limitation of “administering to an eye of the individual (a) an aqueous solution comprising atropine or atropine sulfate and less than about 10% of a degradant of atropine or atropine sulfate formed from degradation of the atropine or atropine sulfate.” Pet. 30–32. As Petitioner points out, both *Chia* and *Akorn* teach their atropine solutions are administered to the eyes of individuals. Pet. 30 (citing Ex. 1003, 2 (participants received atropine sulfate eye drops “once nightly in both eyes”); Ex. 1004, 1–4 (describing “eyedrop instillation” administration by “1 drop topically to the cul-de-sac of the conjunctiva”). *Akorn* expressly states that its solution contains water, Ex. 1003, 2 and Dr. Byrn persuasively testifies that the liquid “eye drops” of *Chia* “are well understood in the art” to be “most commonly aqueous ophthalmic solutions.” Ex. 1002 ¶ 89.

Petitioner asserts that the degradation limit component of this limitation is “simply an inherent property of the atropine or atropine sulfate ophthalmic solution.” Pet. 31 (citing Ex. 1002 ¶ 91). Petitioner relies on the teachings of *Kondritzer* to show this limitation is an inherent property of the composition, i.e., that the limit on the amount of degradation products, such

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as tropic acid, necessarily results from the claimed ophthalmic composition. *See* Pet. 31; Ex. 1002 ¶ 43; Ex. 1005; *see In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011) (determining claim limitation directed to an inherent property of a formulation “adds nothing of patentable consequence”).

For instance, Dr. Byrn testifies that “*Kondritzer* showed that atropine degradation was a predictable function of pH and temperature. Ex. 1005, 1, 4–5. *Kondritzer* derived an equation to predict the pH at which atropine would be most stable for any hydrogen ion concentration. Ex. 1005, 2.” Ex. 1002 ¶ 92. Dr. Byrn also testifies that *Kondritzer* shows in Figure 10 that “at 20° C and pH 5, the half-life of atropine is 266 years; and at 20° C and pH 6, the half-life of atropine is 27 years.” Ex. 1002 ¶ 93. Dr. Byrn utilized *Kondritzer*’s chart in Figure 10 to calculate the time it would take for 10% of atropine to degrade at a pH of 5 and 20° C. *Id.* Dr. Byrn concludes that “at 20° C and pH 5, a POSA would reasonably expect the compositions of claim 1 to comprise 90% atropine for approximately 40.4 years. At these parameters, which fall within the limitations of claim 1, *Kondritzer* shows that atropine would readily exceed the stability requirements of limitation 1[b], which allows for up to 10% degradation.” *Id.* ¶ 93.

We credit Dr. Byrn’s testimony concerning the teachings of *Kondritzer* and the ability of a POSA to predict the amount of degradation of atropine over time. Therefore, we find that Petitioner has shown that the degradation component of this limitation is inherent in the ophthalmic solution of claim 1.

(2) *Buffering Agent*

The heart of the parties' dispute in this case involves whether the cited art teaches "a buffering agent." *See* Pet. 32; PO Resp. 25–41.

Petitioner relies on Akorn as disclosing dibasic sodium phosphate, and monobasic sodium phosphate, which "a POSA would have understood these to be buffering agents that *Akorn* uses to achieve and maintain the desired solution pH." Pet. 32 (citing Ex. 1002 ¶¶ 94–95)

Patent Owner disagrees. Patent Owner asserts that "all grounds critically hinge on using the same 'buffer system' and pH range allegedly disclosed in [*Akorn*]." PO Resp. 30. But, Patent Owner asserts that *Akorn* does not state that it employs a buffering agent to control or maintain pH of its atropine solution, and does not even disclose the actual pH of its solution. PO Resp. 26. Patent Owner also asserts that the phosphate salts disclosed in *Akorn* are not identified as buffering agents, and could not have buffered *Akorn's* solution at the listed pH range. *Id.* at 26–27, 34–35. Dr. Laskar testifies that in listing the pH range of 3.5 to 6.0, *Akorn* is merely showing compliance with the pH limits imposed by the National Formulary of the U.S. Pharmacopeia ("USP") and does not state the pH of the described solution. PO Resp. 1, 33–35.

Akorn describes the ingredients of its formulation as follows.

Each mL of Atropine Sulfate Ophthalmic Solution USP, 1% contains: **Active:** atropine sulfate 10 mg equivalent to 8.3 mg of atropine. **Inactives:** benzalkonium chloride 0.1 mg (0.01%), dibasic sodium phosphate, edetate disodium Hypromellose (2910), monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.

Ex. 1004, 3.

Patent Owner's argument rests on a listed buffering range in the Waterman reference for phosphoric acid that does not encompass a pH of 3.5 to 6.0 as set forth in Akorn. *See* Ex. 2003 ¶ 52; Ex. 1040, 23. As Dr. Laskar testifies, "Waterman Table 8 lists the 'Buffering Range' of Phosphoric acid as '2–3.1, 6.2–8.2.'" Ex. 2003 ¶ 52 (citing Ex. 1040, Table 8). Dr. Laskar testifies:

As the Waterman reference submitted with the petition explains, when selecting a buffer, which acts to maintain a solution pH (e.g., at the pH of maximum stability of the active ingredient), the "primary criteria for selection" are "the pH range and buffer capacity [which is maximal at a pH value equal to the pK_a of the buffer (164)] for the buffer." Ex. 1040, 23 (bracketed in material in original). Waterman states that its "Table 8 lists commonly used buffers along with their pK_a values and optimal pH ranges." *Id.* Waterman Table 8 lists the "Buffering Range" of Phosphoric acid as "2–3.1, 6.2–8.3." *Id.*; Table 8; *see also* paragraph 9 above. In other words, the buffering range of phosphoric acid and its dibasic sodium phosphate and monobasic sodium phosphate salts does not cover or even overlap with a solution of pH of 3.5–6.

Ex. 2003 ¶ 52.

Patent Owner's argument presumes that the pK_a for a particular buffer is set at a particular pH range which is not malleable depending on the conditions of the solution that is being buffered. Waterman itself refutes this presumption. First, Waterman describes the buffering ranges listed in Table 8 as "optimal" pH ranges of $pK_a \pm 1$ indicating some buffering capacity may exist below or above the given ranges. *See* Ex. 1040, 23. Dr. Byrn testifies that the most effective pH range for a buffer is within ± 1 of its pK_a , but "[i]t's not a hard cutoff; it's an effectiveness issue." Ex. 2009, 87:5–12; *see id.* at 88:23–89:19 ($pK_a \pm 1$ covers the most effective buffer range, but it is not a hard cutoff), 91:7–18 (person of skill knows pK_a

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± 1 is not a hard cutoff); 95:11–97:4 (applying the Henderson, Hasselbach equation provides a wider pH buffering range than $pK_a \pm 1$). Dr. Laskar testifies that pK_a changes as a function of temperature. Ex. 1078, 124:5–9. Waterman also states that “[u]se of co-solvents, surfactants, and complexing agents to solubilize a drug may also influence that buffering capacity and final pH of a formulation by altering the effective pK_a of the buffer and/or directly interacting with the buffer components.” Ex. 1040, 24. The evidence of record indicates that the pK_a for a buffer is not static, but depends on the parameters of the solution in which the buffer is used.

As for the specific phosphate buffers used in Akorn and claim 5 of the ’557 patent, Petitioner submitted credible evidence that the lower end of the buffer range for these buffers may be as low as pH 5.4. For instance, in Chapter 4 of the Fifth Edition of the European Pharmacopoeia, with which Dr. Laskar testifies he is familiar and which contains recipes for various buffer solutions, is described a 0.067 molar phosphate buffer solution with a pH of 5.4 that is within the 3.5 to 6.0 pH range set forth in Akorn. *See* Ex. 1081, 6; Ex. 1078, 113:12–118:20; *see also* Ex. 1078, 115:22–116:5 (stating European Pharmacopoeia provides a recipe for an 0.067 molar phosphate buffer solution pH 5.4 within the 3.5 to 6.0 pH range).

Petitioner also presents further evidence of a phosphate buffer with a pH range of 5.8 to 8.0 as set forth in a book titled “Buffers: A guide for the preparation and use of buffer in biological systems,” by Calbiochem, an affiliate of Merck KGaA. *See* Ex. 1082, 1, 2, 25. The excerpt showing the recipe is set forth in a screenshot, which is reproduced below. Ex. 1082, 25.

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6. Phosphate Buffer; pH range 5.8 to 8.0

(a) 0.1 M Sodium phosphate monobasic; 13.8 g/l (monohydrate, M.W. 138.0)

(b) 0.1 M Sodium phosphate dibasic; 26.8 g/l (heptahydrate, M.W. 268.0)

Mix sodium phosphate monobasic and dibasic solution in the proportions indicated and adjust the final volume to 200 ml with deionized water. Adjust the final pH using a sensitive pH meter.

ml of Sodium phosphate, Monobasic	92.0	81.5	73.5	62.5	51.0	39.0	28.0	19.0	13.0	8.5	5.3
ml of Sodium phosphate, Dibasic	8.0	18.5	26.5	37.5	49.0	61.0	72.0	81.0	87.0	91.5	94.7
pH	5.8	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0

The screenshot above shows a recipe and accompanying table for making an aqueous phosphate buffer having a pH between 5.8 and 8.0 by mixing 0.1 M sodium phosphate monobasic with 0.1 M sodium phosphate dibasic in deionized water.

Petitioner further presents evidence from PubChem from the National Institutes of Health on the pK_a values for Monosodium phosphate and disodium hydrogen phosphate. *See* Exs. 1084, 1085. The first publication lists the pK_a for monosodium phosphate as a range from 6.8–7.2 “depending on the physiochemical characteristics during pK_a determination.” Ex. 1084, 7. The second publication lists the pK_a ’s for disodium hydrogen phosphate in the following table, which differ from those set forth in the Waterman reference. Ex. 1085, 8.

3.2.13 Dissociation Constants

$pK_{a1} = 2.15$; $pK_{a2} = 6.83$; $pK_{a3} = 12.38$ (phosphoric acid), all at 25 °C

Sigma-Aldrich; Sodium phosphate dibasic. S9763. Sigma-Aldrich, St. Louis, MO. Available from, as of Nov 30, 2006: <https://www.sigmaaldrich.com/catalog/search/ProductDetail/SIAL/S9763>

The table is table 3.2.13 from the PubChem listing for Disodium hydrogen phosphate, showing pK_a values for dissociation of 2.15, 6.83, and 12.38 at 25° C.

With this record evidence in mind, we turn to what a POSA would glean from reviewing Akorn. Dr. Byrn testifies that Akorn discloses standard buffering agents, including dibasic sodium phosphate, also known as disodium hydrogen phosphate, and monobasic sodium phosphate, also known as sodium dihydrogen phosphate, that have been shown in the evidence just discussed to be able to buffer Akorn's formulation at least in the upper part of the cited pH range. Ex. 1002 ¶¶ 94–95 (citing Ex. 1019, 52; Ex. 1026, 4–5). We disagree with Dr. Laskar's reliance solely on the Waterman reference as disclosing a buffering range for phosphate salts that “has no overlap with a solution pH of 3.5 to 6.0,” and do not credit his conclusion that a POSA would understand this lack of overlap “to completely contradict Dr. Byrn's assertions that these phosphate salts represent a ‘common buffer’ that was used in EX1004 ‘to maintain a pH of 3.5 to 6.0.’” See Ex. 2003 ¶ 78.

We do not agree with Dr. Laskar's criticism that Akorn does not disclose buffers. See Ex. 2003 ¶¶ 71–72. Dr. Laskar testifies that Akorn does not disclose any buffers. *Id.* Dr. Laskar further testifies:

To the contrary, the disclosure of EX1004 is consistent with the direction provided in Remington and the state of the art in 2015 regarding atropine aqueous ophthalmic solutions. Everything I have read in EX1004 is consistent with the state of the art before 2015, which was to avoid using a buffer or buffering agent in the acidic solution of storage within the boundaries (pH 3.5–6.0) imposed by the USP.

Ex. 2003 ¶ 71.

We find, however, that Dr. Laskar's statements concerning the state of the art in 2015, including about the teachings of the Remington reference, are not sufficiently supported by record evidence. For instance, Dr. Laskar premises his conclusion concerning the state of the art in 2015 that buffers

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should not be used for atropine solutions, as informed by the Remington reference Dr. Laskar calls the formulator's "bible," on the mistaken belief that the phosphate buffers listed in Akorn cannot buffer below a pH of 6.0. *See generally* Ex. 2003 ¶¶ 45–69. Remington, however, expressly lists phosphate salts in a suggested ophthalmic solution for atropine, but Dr. Laskar states, without support other than the Waterman reference, that "[n]either one of these phosphate salts, alone or in the disclosed combination, is a buffering agent to provide a pH of from about 4.8 to about 6.4. Nor do they provide, alone or in combination, a buffer for a solution having a pH no lower than 3.5 and no higher than 6.0." *Id.* ¶ 50.

As set forth above, we do not agree that the phosphate salts listed in Remington do not buffer at a pH of 6.0 or below. We do not understand Dr. Laskar's statement that these buffers also do not provide a pH no greater than about 6.4. Dr. Laskar testifies that it is difficult to change the pH of a solution by adjusting the ratio of acid to conjugate base of a buffer from a 50:50 ratio, *see* Ex. 2003 ¶ 59, and states that "[i]n Remington, for example, the atropine ophthalmic vehicle uses somewhat more than twice as much monobasic phosphate as dibasic phosphate on a molar basis, but this alters the pH only by about 0.3 pH units," *id.* Dr. Laskar concludes, however, that the phosphate buffer system listed in claim 5 of the '577 patent, the same buffering pair listed in Akorn, *can* provide a pH no greater than about 6.4 by utilizing "extremely large and counterintuitive variations from standard buffer protocols" to be able to "buffer near the limits of an agent's buffering range." *Id.* Patent Owner cannot have it both ways; phosphate buffers listed in Remington in the suggested atropine solution cannot be said to not buffer, while phosphate buffers listed in claim 5 of the '557 patent, which do not have any particular amount or ratio of acid to base listed, do perform the

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function of a buffer that provides a pH of no greater than about 6.4. *See* Ex. 1002 ¶ 59 (claim 7 of the '787 patent).

We agree with Dr. Byrn that Remington does recommend the use of buffers to maintain the pH at the appropriate level. Ex. 1002 ¶ 50 (citing Ex. 1019, 52–54). In discussing ophthalmic preparations, Remington states:

Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. . . .

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimum for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability, but minimized so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily.

Ex. 1019, 54.

Remington is recommending a buffer to stabilize an ophthalmic solution for the product's shelf life, but also recommends a balance with the buffers capacity to prevent any resistance to adjustment by tear fluid when the ophthalmic solution is applied to the eye to provide patient comfort and compliance. Contrary to Dr. Laskar's testimony, the record evidence shows that buffers are recommended for ophthalmic solutions to maintain shelf life.

Akorn also discloses a pH range of 3.5 to 6.0 for its formulation that overlaps with the pH range at which atropine was known to be most stable, pH 3–5. *Id.* at ¶ 93; *see* Ex. 2003 ¶ 45 (Dr. Laskar admits that “The United States Pharmacopeia/National Formulary had long required atropine sulfate ophthalmic solution to be packaged for storage at a solution pH no greater than 6.0 and no less than 3.5.”). Patent Owner takes issue with the fact that we don’t know the exact pH of Akorn’s formulation. *See* Ex. 2003 ¶ 74. We don’t find this argument persuasive as Akorn teaches a particular pH range for its formulation for 1% atropine, which informs a POSA of the appropriate pH range, if not a particular point within the range. The appropriate pH range set forth in Akorn overlaps with the claimed pH ranges in dependent claims 16 and 20, and there is no dispute that pH is a result effective variable for the stability of an atropine solution and finding the optimum pH value for an atropine solution is within the level of ordinary skill of the art. *See* Ex. 1002 ¶¶ 96–98; Ex. 1005 (showing how to predict half-lives of atropine solutions at various pH values and temperatures); Ex. 2003 ¶¶ 38, 61, 62; Ex. 1078, 143:11–144:5 (stating “a POSA would be able to prepare a buffer at pHs within that range of 4.8 to 6.4). This evidence is sufficient to support a case of obviousness. *See E.I. DuPont de Nemours, Inc. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence” of teaching away, unexpected results, or other pertinent evidence of nonobviousness.”).

Patent Owner alleges criticality of the claimed pH range set forth in the claims when providing an overview of the ’557 patent. *See* PO Resp. 15–19; Ex. 2003 ¶¶ 156–158. Patent Owner argues that the inventors

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discovered that “using a buffer was critical to atropine stability” for the claimed low dose in the claimed range. PO Resp. 18. This is not appropriate objective evidence of nonobviousness to rebut Petitioner’s proof of overlapping ranges between the prior art and the claimed pH range because the result of using a buffer regardless of whether the problem of the stability of atropine at low doses was unexpected, pH stability for the range, was not unexpected. The buffer is just doing exactly what a buffer does as recognized: viz., maintaining pH. See Ex. 1038, 2 (stating “primary purpose of a buffer is to control the pH of the solution”). The fact that the claimed range for a stable low dose atropine solution substantially overlapped with the USP stated range for atropine solutions is also not surprising or unexpected.

(3) Reason to Combine with a Reasonable Expectation of Success

The Petitioner asserts that a POSA would have been motivated to formulate lower-concentration atropine formulations for the treatment of the progression of myopia to reduce “side effects without significant loss of efficacy.” Pet. 25 (citing Ex. 1002 ¶¶ 67–70). Recognizing the side effects of higher concentration atropine solutions, such as photophobia, cycloplegia, and mydriasis, causing poor patient compliance, Petitioner asserts that Chia studied lower dose atropine compositions and concluded that “a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.” *Id.* at 25 (citing Ex. 1002 ¶¶ 70–71; Ex. 1003, 1, 7, 8). This conclusion, Petitioner asserts would have motivated a POSA “to use a buffering system to achieve a stable, ready-to-use formulation for that treatment.” *Id.* (citing Ex. 1003, 8; Ex. 1002 ¶¶ 70–71).

Petitioner further reasons that because using atropine to treat myopia requires long-term treatment, a POSA “would have been motivated to use buffers to increase the stability (i.e., minimize the formation of degradants) of low-concentration solutions.” Pet. 26 (citing Ex 1003, 1; Ex. 1002 ¶¶ 73–78). In light of the teachings of Kondritzer, Petitioner states that a POSA would have known that atropine’s stability was pH dependent, and “[i]n selecting a suitable buffer system for long-term stability of atropine solutions, a POSA would have looked to FDA-approved atropine ophthalmic solutions,” such as Akorn. Pet. 26–27 (citing Ex. 1005; Ex. 1002 ¶¶ 65, 73–78). In addition to shelf life, Petitioner asserts a POSA also would have been concerned about patient comfort and compliance with using the low-concentration atropine product and would know that the pH for optimum patient comfort is the same pH as tear fluid, about 7.4. *Id.* at 27–28. In balancing stability of atropine, which is most stable at a pH from 3 to 5 according to Kondritzer, Petitioner asserts that “a POSA would have been motivated to increase the long-term stability of *Chia*’s low-concentration atropine at pHs closer to the clinically desirable pH of 7.4.” *Id.* at 28 (citing Ex. 1002 ¶ 78). Petitioner asserts that a POSA would have had a reasonable expectation of success in doing so by using buffers, a common component in ophthalmic compositions, to target “the higher end of Akorn’s disclosed pH range in order to optimize stability in view of patient comfort” *Id.* at 28.

Patent Owner responds that the low-concentration atropine formulations did not contain buffers and that the state of the art in 2015 taught excluding the use of buffers. *See* PO Resp. 41–46. We have addressed Patent Owner’s argument that the state of the art in 2015 for ophthalmic solutions did not teach buffers. As we found above, the record

evidence such as Remington shows that buffers are recommended for ophthalmic solutions to maintain shelf life.

We also note that the prior art references such as Chia described studies to determine the safety and efficacy of low-dose atropine solutions and were not commercially available formulations that must meet FDA requirements for safety and efficacy. Chia specifically states that “[a]tropine 0.01% is currently not commercially available.” Ex. 1003, 8.

Patent Owner also asserts that adding a buffer would decrease patient comfort by maintaining a low pH of the atropine solution when administered, causing increased tearing which would undermine efficacy by washing away the atropine. PO Resp. 44–46. We do not find this argument persuasive. As Remington explained, a POSA must choose a buffer to stabilize an ophthalmic solution, but also balance the shelf-life of the solution with a buffering capacity that allows a patient’s tears to easily overcome an uncomfortable acidic pH of the ophthalmic solution. *See* Ex. 1019, 54. As Remington states, “[b]uffer capacity is the key,” and “buffer capacity should be adequate for stability, but minimized so far as possible to allow the overall pH of the tear fluid to be disrupted only momentarily.” *Id.* Buffering does not impede patient comfort when buffer capacity is properly assessed.

We agree with Petitioner and Dr. Byrn that “a POSA would have been motivated to formulate low-concentration atropine solutions that could be administered at pHs closer to those that provided optimal patient compliance and clinical efficacy, but that could also remain stable over long periods of time.” Ex. 1002 ¶ 78. We determine that Petitioner has shown an appropriate reason to combine the teachings of Chia, Akorn, and Kondritzer

to arrive at the composition of claim 1 with a reasonable expectation of success.

(4) Conclusion

We determine that Petitioner has shown by a preponderance of the evidence that claim 1 of the '557 patent would have been obvious over Chia, Akorn, and Kondritzer.

d) Dependent Claims 2–7, and 11–20

Dependent claims 2 and 3 each recite the method of claim 1 with specified ranges or concentrations of atropine or atropine sulfate solutions. *See* Ex. 1001, 100:19–27. Petitioner relies on Chia's teaching of 0.01% atropine, which is within claim 2's range and is the exact amount as claimed in claim 3, to establish that these dependent claims would have been obvious as well. *See* Pet. 32–34 (citing Ex. 1002 ¶¶ 96–98). Petitioner also points to Chia's express motivation to formulate ophthalmic compositions with low atropine concentrations. Pet. 33 (citing Ex. 1002 ¶ 99).

Patent Owner does not address these additional limitations apart from its arguments as to claim 1. The reasons that we set forth above for the determination that claim 1 would have been obvious equally apply here. We determine that Petitioner has shown by the preponderance of the evidence on the record before us that claims 2 and 3 would have been obvious over Chia, Akorn, and Kondritzer.

Claims 4 and 5 further define the buffering agent of claim 1 to include a phosphate buffering agent for claim 4 and "sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof" for claim 5, which Petitioner asserts Akorn teaches. *See* Pet. 34 (citing Ex. 1002 ¶¶ 103–107; Ex. 1004, 3). Patent Owner reasserts the same argument that it raised with

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respect to claim 1, namely, that Akorn does not teach the claimed phosphate buffers. *See* PO Resp. 57. We have addressed Patent Owner’s arguments with respect to claim 1 and found that Akorn does teach the claimed phosphate buffers.

Claim 6 further requires a tonicity adjusting agent, and claim 7 further defines the tonicity agent as a halide salt of a monovalent cation. Ex. 1001, 100:37–40. Petitioner asserts that “[a] POSA would have recognized that decreasing the concentration of atropine sulfate from *Akorn*’s 1% atropine sulfate solution to *Chia*’s 0.01% atropine sulfate solution would require the addition of a tonicity adjusting agent to maintain eye comfort,” due to a reduction in the amount of salt in the solution. Pet. 35 (citing Ex. 1002 ¶¶ 110–112). Petitioner also asserts that sodium chloride, a halide salt of a monovalent cation, is a very common tonicity adjusting agent. *Id.* (citing Ex. 1002 ¶¶ 111–112; Ex. 1036, 1–3; Ex. 1019, 54).

Patent Owner responds that Petitioner has not shown that a reduction from 1% to 0.01% atropine sulfate will make enough difference in the osmolarity to be material to the tonicity of the solution, and Petitioner failed to account for the existing tonicity of Akorn’s formulation. PO Resp. 57.

Dr. Byrn explains tonicity and that “isotonicity always is desirable and particularly is important in intraocular solutions.” Ex. 1002 ¶ 110 (citing Ex. 1019, 54). Dr. Byrn then testifies that a reduction in the concentration of atropine sulfate, a salt, from 1% to 0.01 % would require a tonicity adjusting agent for eye comfort. *Id.* We credit Dr. Byrn’s testimony as it is reasonable that a 100-fold decrease in the concentration of atropine sulfate in the solution would require some tonicity adjustment.

Patent Owner asserts that “Petitioner has not demonstrated motivation to buffer the solution at an acidic pH, much less the pH recited in these

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dependent claims [from about 3.8 to about 6.4 for claim 16 and a pH of less than 5 for claim 20], because this was expected to decrease patient comfort without any expected stability benefit.” PO Resp. 55. We have addressed these arguments above and found them unpersuasive. *See* Section II.D.4.c)(2).

Patent Owner does not address the additional limitations of claims 11–15 and 17–19 apart from its arguments as to claim 1. Claims 11, 12, and 13 further require, respectively, a preservative, in a particular concentration, and a list of particular preservatives, which Chia and/or Akorn teach. *See* Pet. 36–37 (citing Ex. 1002 ¶¶ 115–120; Ex. 1003, 2; Ex. 1022, 1–2; Ex. 1023, 1). Claim 14 further requires that the stabilized ophthalmic composition is “essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof,” which Petitioner asserts is taught by the absence of these ingredients in Chia and Akorn. *See* Pet. 37 (citing Ex. 1002 ¶¶ 122–126; Ex. 1003; Ex. 1004, 3; Ex. 1019, 52). Claim 15 further requires the aqueous solution is sterile, which Petitioner asserts is taught by Akorn and Chia. Pet. 37–38 (citing Ex. 1002 ¶¶ 129–131; Ex. 1004, 3; Ex. 1003, 2; Ex. 1019, 52). Claim 17 further requires the aqueous solution is an ophthalmic composition, which Petitioner asserts is taught by Chia and Akorn. Pet. 40–41 (citing Ex. 1002 ¶¶ 143–144; Ex. 1003, 1–2; Ex. 1004, 3). Claims 18 and 19 further require administration at least once a day and once a day, respectively, which Petitioner asserts is taught by Chia and Akorn. *See* Pet. 41 (citing Ex. 1002 ¶¶ 147–150; Ex. 1003, 2; Ex. 1004, 1–2).

We have reviewed Petitioner’s assertions in the Petition concerning claims 11–15 and 17–19 and Dr. Byrn’s testimony in support, and determine

that Petitioner has shown by a preponderance of the evidence that these claims would have been obvious over Chia, Akorn, and Kondritzer.

E. Remaining Grounds

Because we have determined that all challenged claims are unpatentable as obvious over Chia, Akorn, and Kondritzer, we need not reach the issue of whether these same claims are also unpatentable under Grounds 2 and 3. Therefore, we do not reach these grounds.

III. CONCLUSION¹⁴

For the foregoing reasons, we conclude Petitioner has shown by a preponderance of the evidence that claims 1–7 and 11–20 of the ’557 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Patent Owner’s Motion to Exclude Evidence is *denied*;

FURTHER ORDERED that claims 1–7 and 11–20 of U.S. Patent No. 10,888,557 B2 have been shown by a preponderance of the evidence to be unpatentable under 35 U.S.C. § 103; and

¹⁴ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner’s attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1–7, 11–20	103	Chia, Akorn, Kondritzer	1–7, 11–20	
1–7, 11–20	103	Chia, Akorn, Lund ¹⁵		
1–7, 11–20	103	Akorn, Wu, Kondritzer ¹⁶		
Overall Outcome			1–7, 11–20	

¹⁵ Because we find these claims are unpatentable over Chia, Akorn, and Kondritzer, we do not determine their patentability under this ground.

¹⁶ Because we find these claims are unpatentable over Chia, Akorn, and Kondritzer, we do not determine their patentability under this ground.

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(12) **United States Patent**
Ostrow et al.

(10) **Patent No.:** **US 10,842,787 B2**
(45) **Date of Patent:** ***Nov. 24, 2020**

- (54) **OPHTHALMIC COMPOSITION**
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- (72) Inventors: **Gregory I. Ostrow**, San Diego, CA (US); **Kenneth J. Widder**, Rancho Santa Fe, CA (US); **David S. Baker**, Carlsbad, CA (US); **Harun Takruri**, Newport Beach, CA (US)
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- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- This patent is subject to a terminal disclaimer.
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- § 371 (c)(1),
(2) Date: **Oct. 20, 2017**

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- (57) **ABSTRACT**

Provided herein is an ophthalmic composition. In some embodiments, the ophthalmic composition includes a low concentration of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. Further disclosed herein include an ophthalmic composition including a low concentration of an ophthalmic agent and deuterated water. Also disclosed herein are methods of arresting or preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described herein.

19 Claims, 13 Drawing Sheets

Eyenovia Exhibit 1001

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Fig. 1A

		Weeks					
	Temp (°C)	0	1	1.571429	2.142857	3.428571	6.571429
T1	25	0.08			0.88		2.81
T2	40	0.08		3.47		4.48	

Fig. 1B

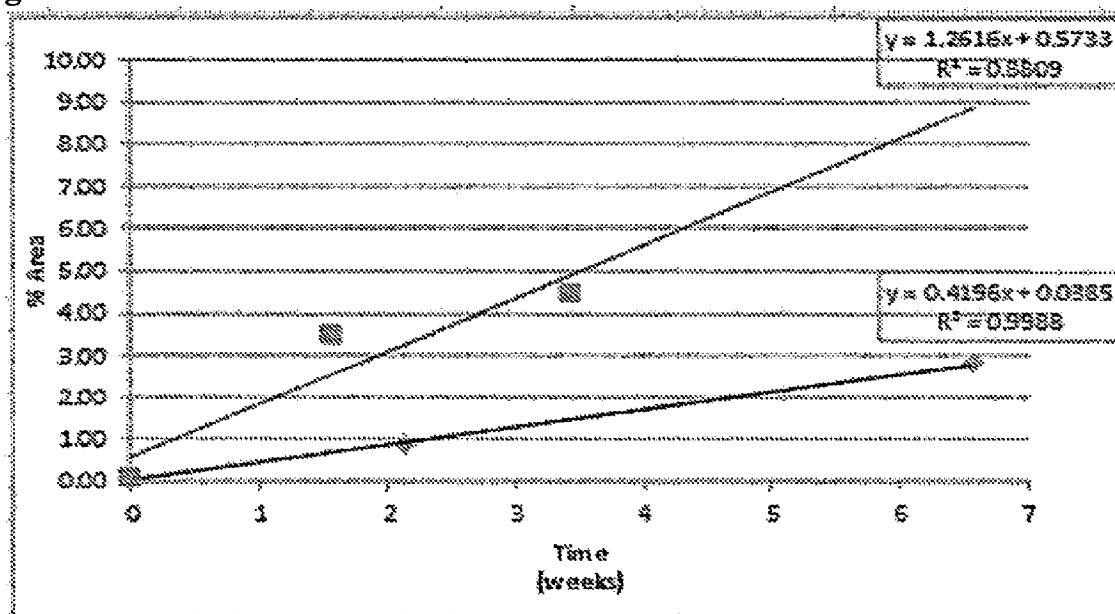


Fig. 1C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	1.24844	at 40C	0.4	0.1
rate	0.60617	at 30C	0.8	0.2
rate	0.41477	at 25C	1.2	0.3
rate	0.07932	at 2-8C	6.3	1.6
rate	0.00694	at -20C	N/A	N/A

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Fig. 2A

Weeks						
	Temp (°C)	0	1	2.142857	4	6.571429
T1	25	0.08		0.9		2.8
T2	60	0.08	10.5		11.3	

Fig. 2B

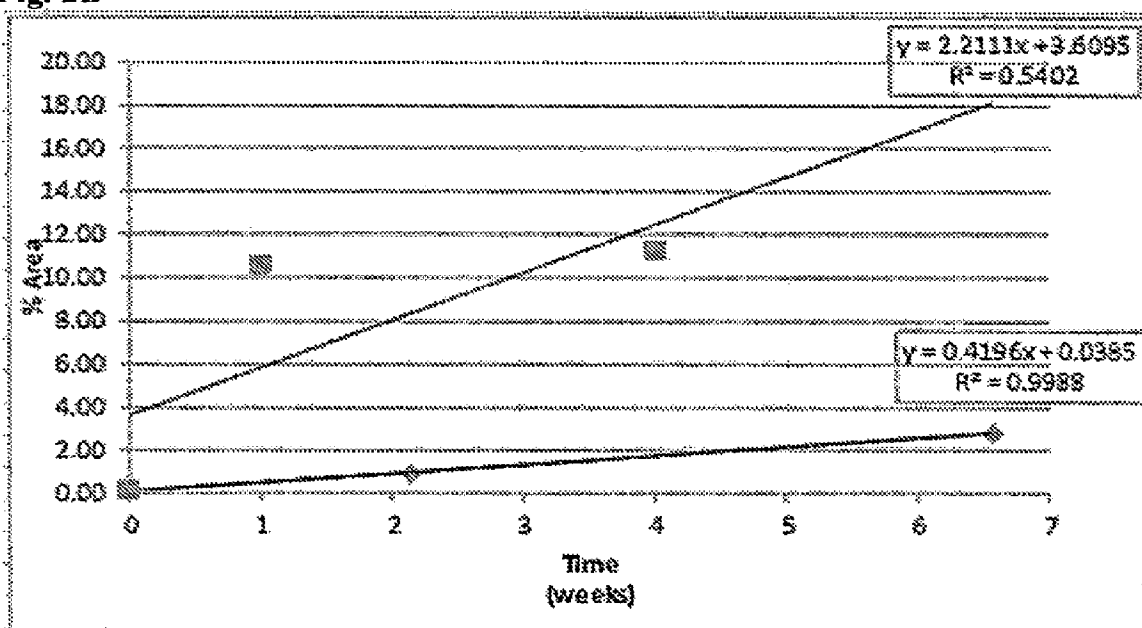


Fig. 2C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	0.63876	at 40C	0.6	0.1
rate	0.54051	at 30C	0.9	0.2
rate	0.41627	at 25C	1.2	0.3
rate	0.13331	at 2-8C	3.8	0.9
rate	0.02493	at -20C	N/A	N/A

Fig. 3

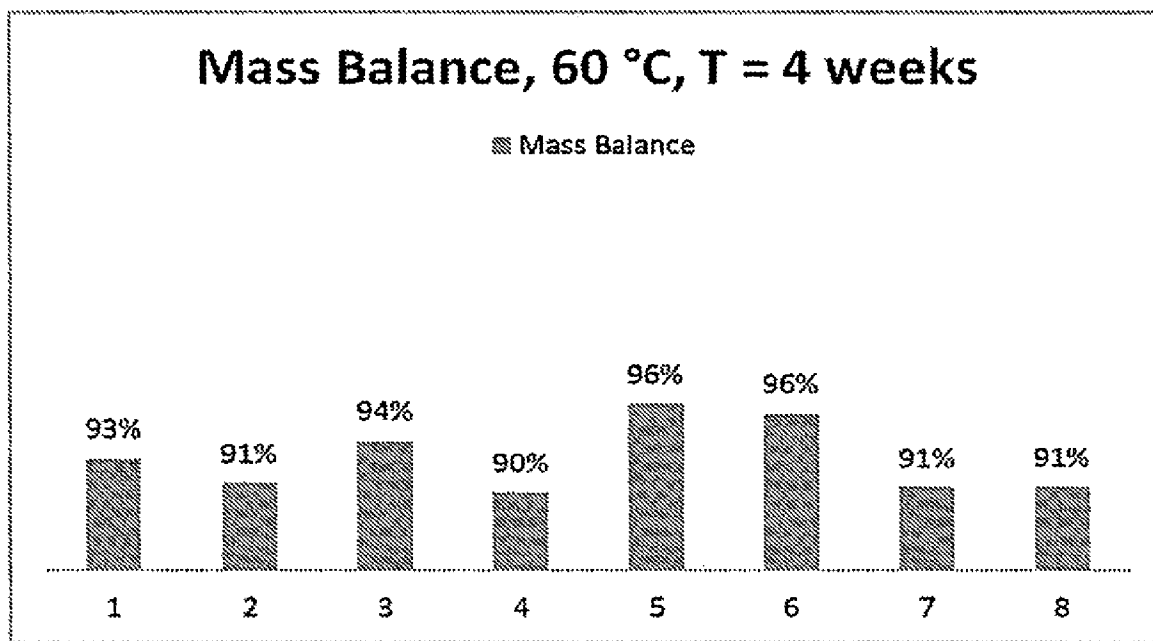


Fig. 4

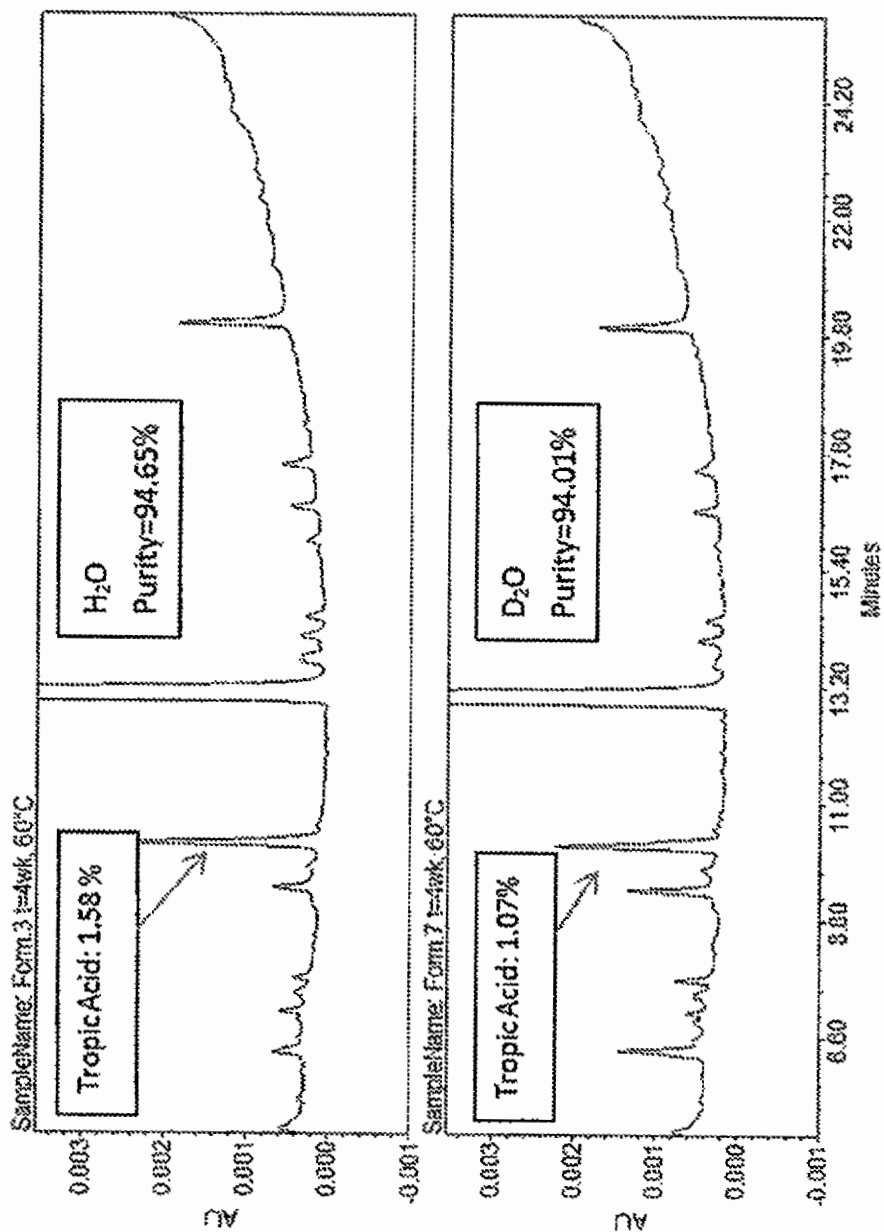


Fig. 5

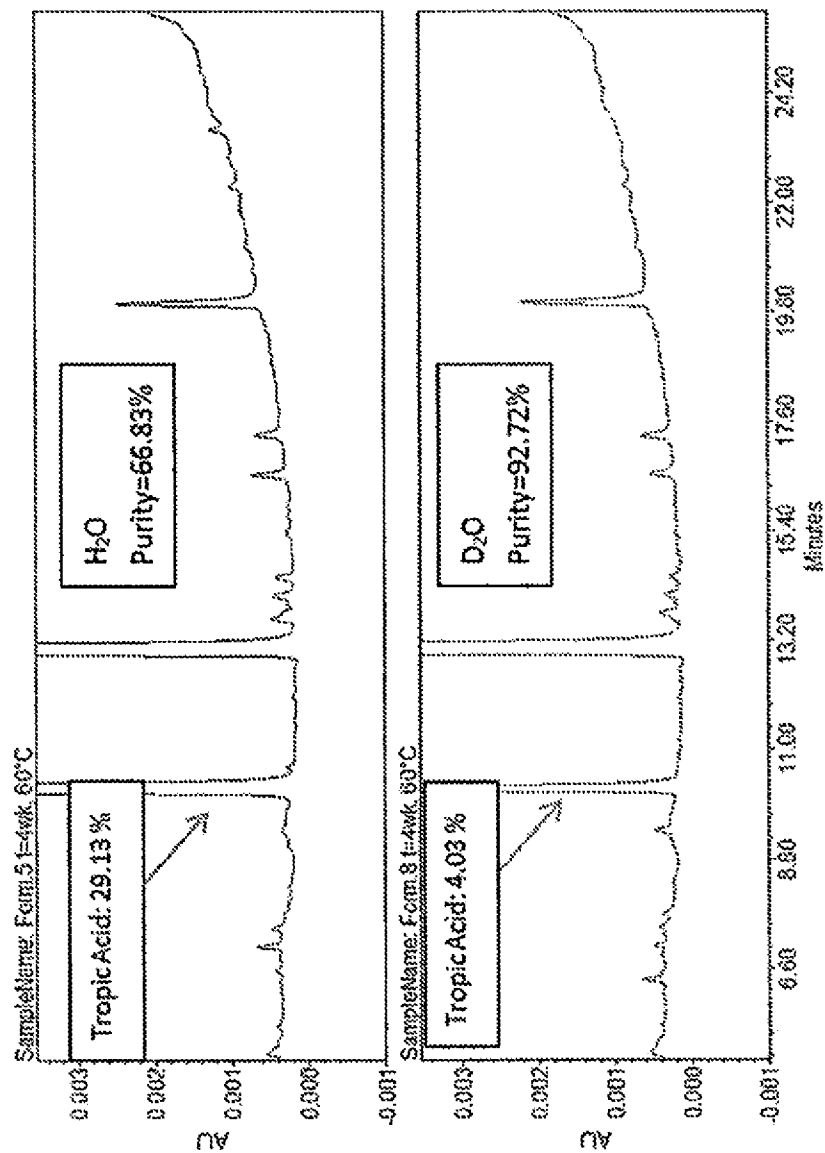


Fig. 6

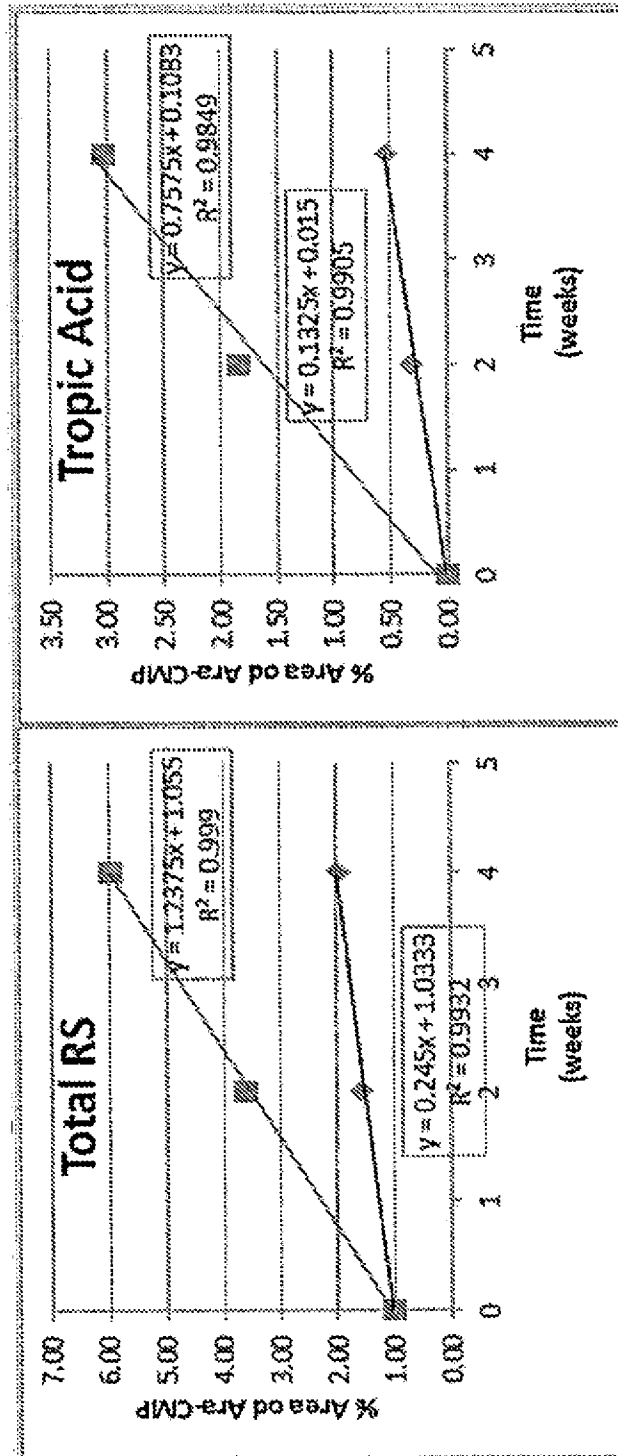


Fig. 7

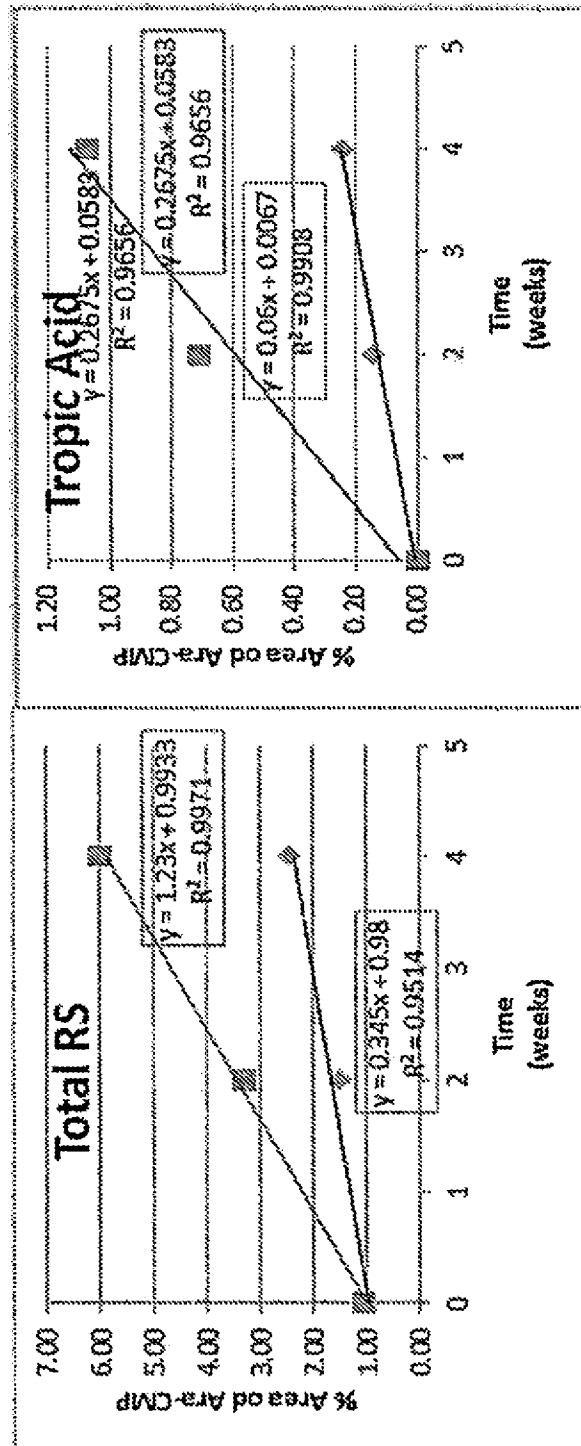


Fig. 8

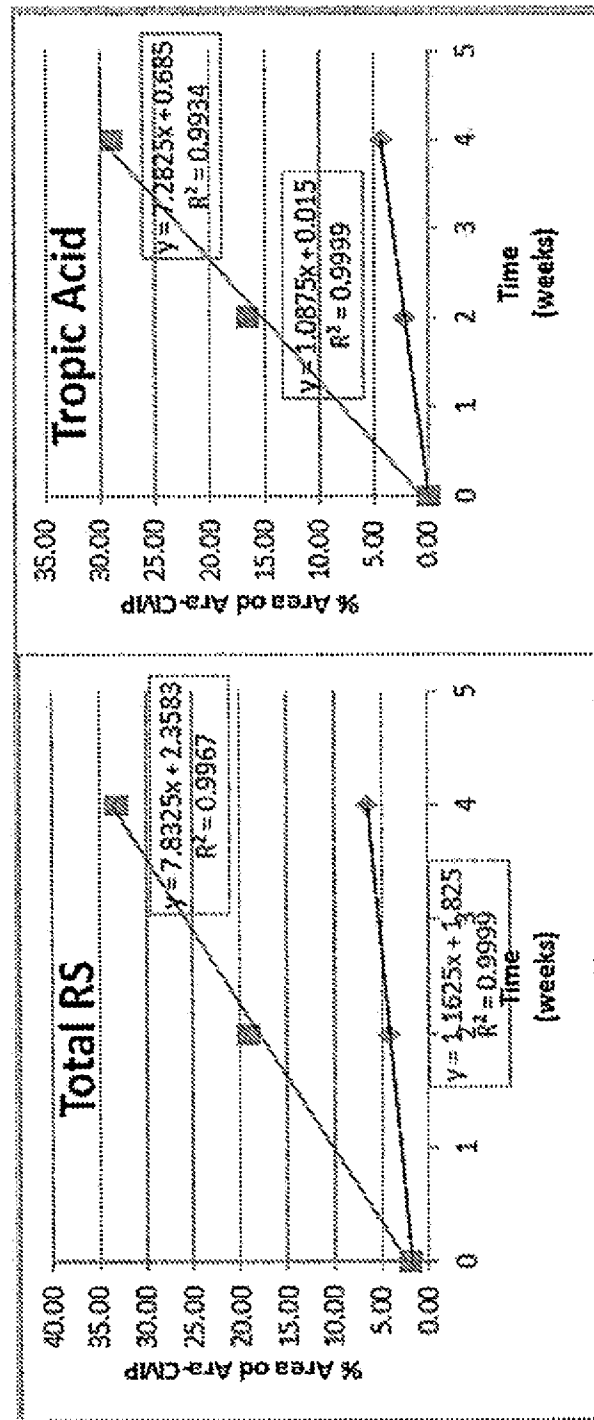


Fig. 9

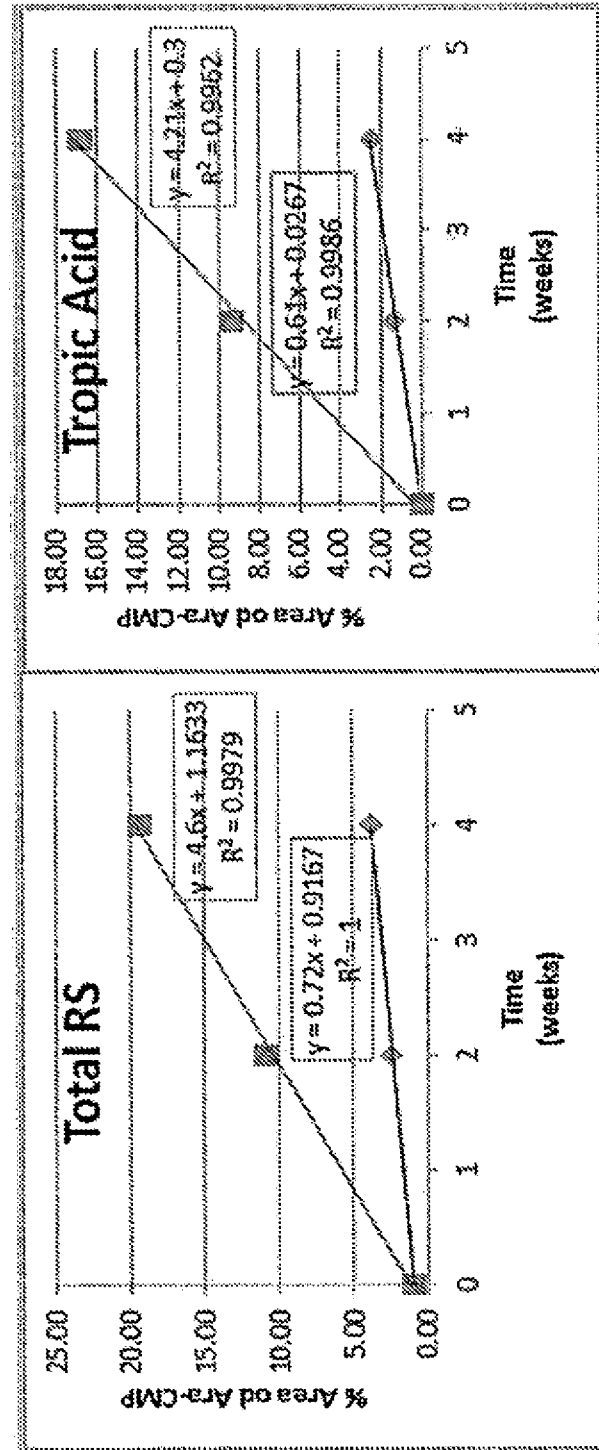


Fig. 10

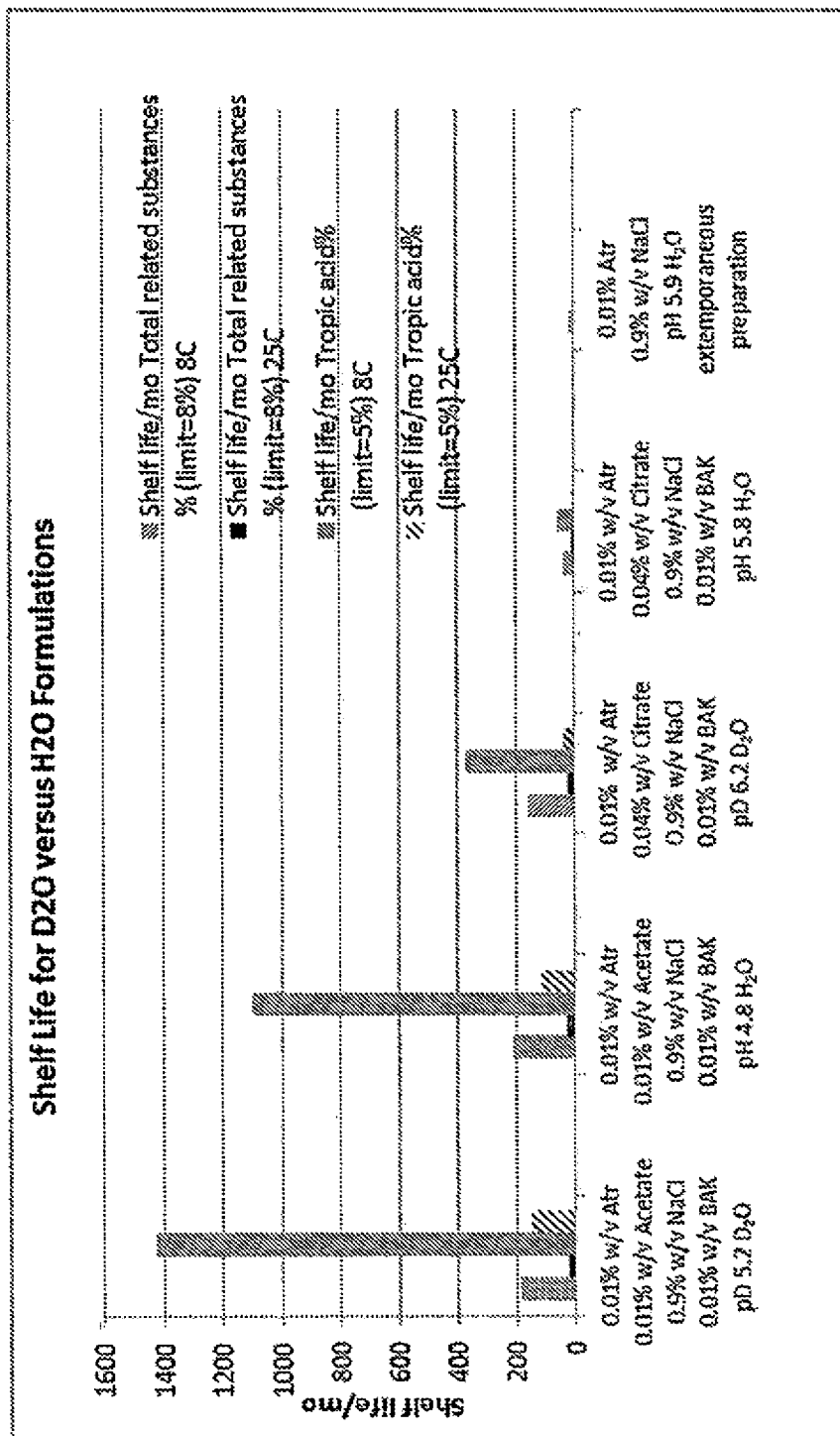


Fig. 11A

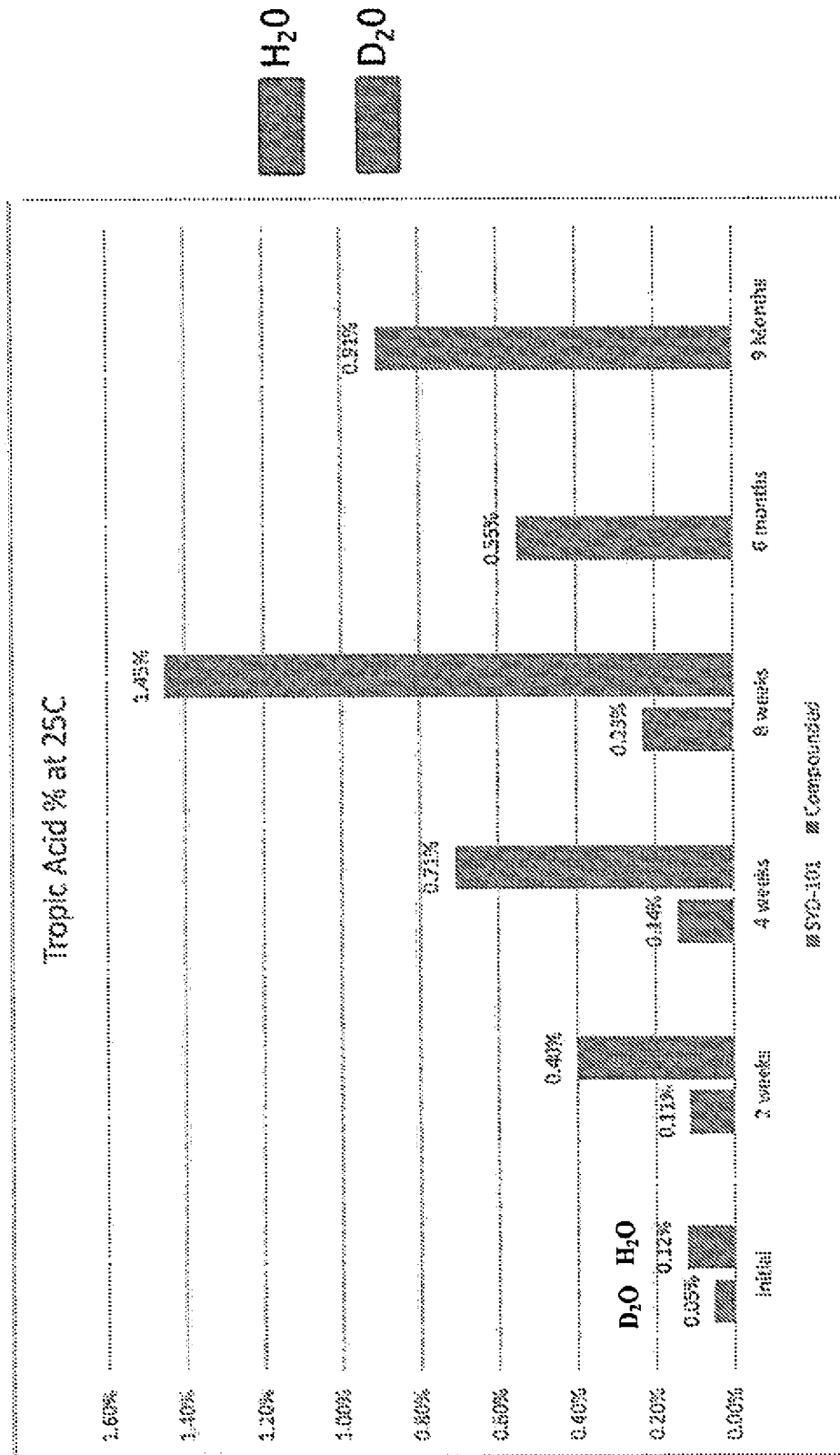


Fig. 11B

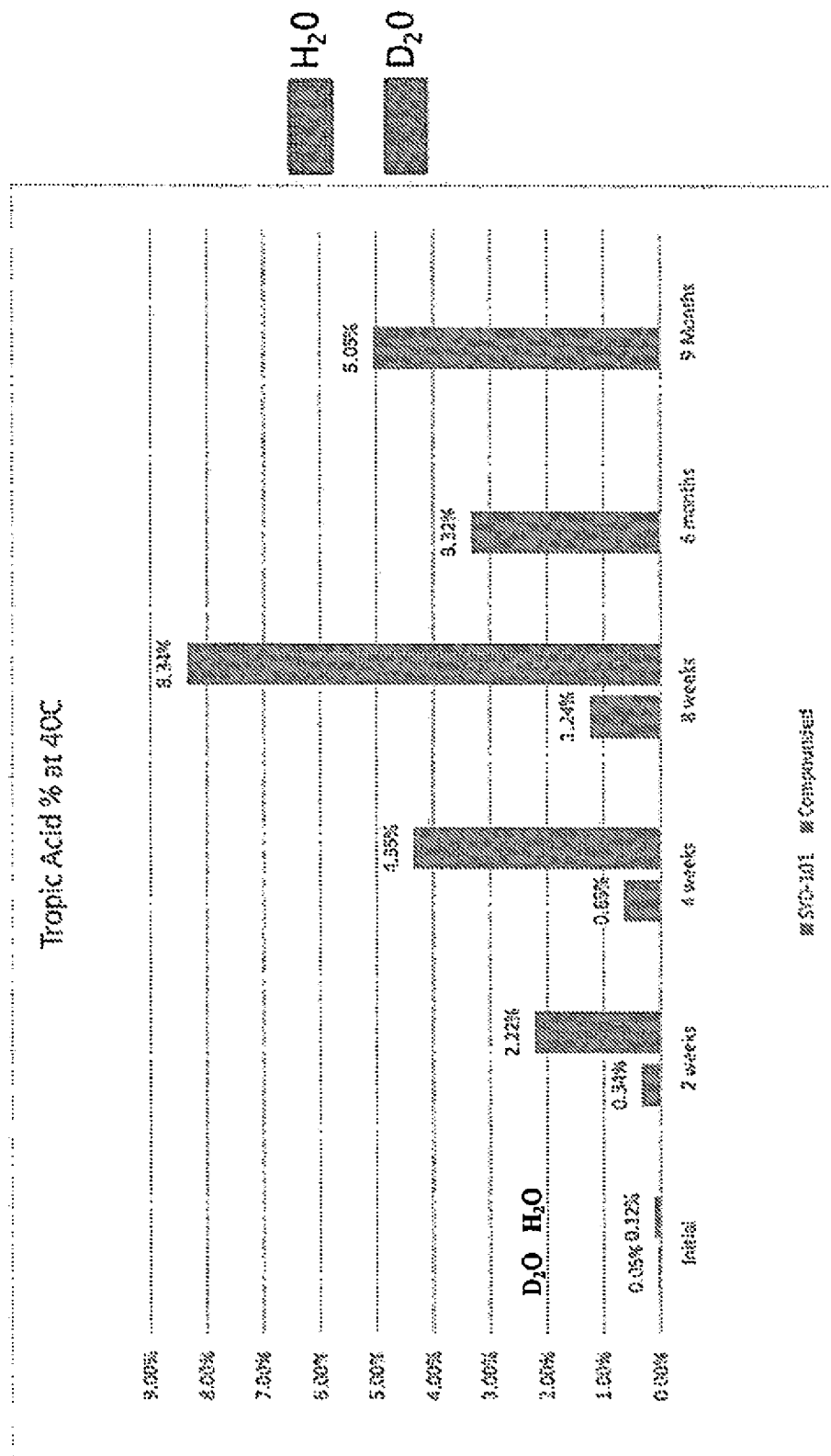


Fig. 11C



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OPHTHALMIC COMPOSITION

CROSS-REFERENCE

This application is filed pursuant to 35 U.S.C. § 371 as a United States National Phase Application of International Application No. PCT/US2016/029222, filed Apr. 25, 2016, which claims the benefit of U.S. Provisional Patent Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2016/029222 is a continuation-in-part of U.S. application Ser. No. 14/726,139, filed May 29, 2015, now U.S. Pat. No. 9,421,199, and is a continuation-in-part of PCT Application No. PCT/US2015/037249, filed Jun. 23, 2015. U.S. application Ser. No. 14/726,139 claims the benefit of U.S. Provisional Patent Application No. 62/151,926, filed Apr. 23, 2015; PCT Application No. PCT/US2015/037249 is a continuation-in-part of U.S. patent Ser. No. 14/726,139, now U.S. Pat. No. 9,421,199, and claims the benefit of U.S. Provisional Patent Application No. 62/151,926, filed Apr. 23, 2015, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE DISCLOSURE

Pharmaceutical formulations have an expiration date which is based on the degradation of the active ingredient.

SUMMARY OF THE DISCLOSURE

Provided herein are ophthalmic compositions. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.

In some embodiments, provided herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist does not extend singlet oxygen lifetime.

In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, scopolamine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the muscarinic antagonist quenches photogenerated singlet oxygen species in the composition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, scopolamine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.

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In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.8, less than about 7.7, less than about 7.6, less than about 7.5, less than about 7.4, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.9, less than about 6.8, less than about 6.7, less than about 6.6, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6.

In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. As described in this disclosure, the percentage of the ophthalmic agent in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. As described in this disclosure, the potency of the ophthalmic agent in the composition after storage is based on the potency of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some embodiments, the storage condition has a storage temperature of about 25° C. In some embodiments, the storage condition has a storage temperature of about 40° C. In some embodiments, the storage condition has a storage temperature of about 60° C.

In some embodiments, the storage condition has a relative humidity of about 60%. In some embodiments, the storage condition has a relative humidity of about 75%.

In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.5% of major degradant based on the concentration of the ophthalmic agent after

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extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid. As described in this disclosure, the percentage of the primary degradant in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the composition is in a form of an aqueous solution.

In some embodiments, the composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some embodiments, the composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE). In some cases, the material of the plastic container comprises polypropylene.

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In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

In some embodiments, the composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, NaOD, CD₃COOD, or C₆D₅O₇.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the ophthalmically acceptable carrier further comprises at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

In some embodiments, the ophthalmic composition comprises one of: less than 60% of H₂O, less than 55% of H₂O, less than 50% of H₂O, less than 45% of H₂O, less than 40% of H₂O, less than 35% of H₂O, less than 30% of H₂O, less than 25% of H₂O, less than 20% of H₂O, less than 15% of H₂O, or less than 10% of H₂O.

In some embodiments, the ophthalmic composition comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O.

In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use.

In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

In some embodiments, the ophthalmic composition does not comprise water-hydrolyzable derivatives of α -amino or α -hydroxy-carboxylic acids.

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In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.

In some embodiments, the ophthalmic composition is a solution.

In some embodiments, disclosed herein is a method of treating an ophthalmic disorder comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of treating an ophthalmic disorder, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, disclosed herein is a method of arresting myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. Also described herein is a method of preventing myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of arresting or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is

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stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, disclosed herein is an ophthalmic solution that comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic solution has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the ophthalmic solution comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O. In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years. In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %. In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a

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combination thereof. In some embodiments, the muscarinic antagonist is atropine or atropine sulfate.

In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

In some embodiments, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some embodiments, the storage condition has a storage temperature of one of: about 25° C., about 40° C., or about 60° C. In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C.

In some embodiments, the storage condition has a relative humidity of about 60% or about 75%.

In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihy-

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drogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some embodiments, the ophthalmic composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE).

In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some embodiments, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

In some embodiments, the ophthalmic composition comprises one of: less than 60% of D₂O, less than 55% of D₂O, less than 50% of D₂O, less than 45% of D₂O, less than 40% of D₂O, less than 35% of D₂O, less than 30% of D₂O, less than 25% of D₂O, less than 20% of D₂O, less than 15% of D₂O, or less than 10% of D₂O.

In some embodiments, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% of D₂O. In some embodiments, ophthalmic composition is essentially free of D₂O.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

Other features and technical effects of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

FIG. 1A-FIG. 1C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 40° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

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FIG. 2A-FIG. 2C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 60° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

FIG. 3 illustrates mass balance at 4 weeks and at 60° C. condition for atropine sulfate formulations disclosed in Example 9.

FIG. 4 illustrates atropine sulfate (0.010%) formulation stability in acetic acid. The atropine sulfate formulation is formulated with acetic acid and either with H₂O (top panel, Formulation 3) or D₂O (bottom panel, Formulation 7). Formulation 3 has a pH of 4.8 and Formulation 7 has a pD of 5.2. Both formulations are stored at 60° C. for 4 weeks prior to analysis.

FIG. 5 illustrates atropine sulfate (0.01%) formulation stability in citric acid. The atropine sulfate formulation is formulated with citric acid and either with H₂O (top panel, Formulation 5) or D₂O (bottom panel, Formulation 8). Formulation 5 has a pH of 5.8 and Formulation 8 has a pD of 6.2. Both formulations are stored at 60° C. for 4 weeks prior to analysis.

FIG. 6 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 4) at pH 4.8 in H₂O.

FIG. 7 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 7) at pD 5.2 in D₂O.

FIG. 8 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 5) at pH 5.8 in H₂O.

FIG. 9 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 6) at pH 5.8 in H₂O.

FIG. 10 illustrates estimated shelf lives for D₂O and H₂O formulations disclosed in Examples 11 and 12.

FIG. 11A-FIG. 11C illustrate stability of atropine sulfate formulation 8 in H₂O and D₂O under three storage conditions.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure recognizes that there is a need for a stabilized ophthalmic composition with extended shelf life upon storage. The present disclosure also recognizes that there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active agents. The present disclosure further recognizes that there is a need for an ophthalmic composition that provides convenient and effective delivery of a muscarinic antagonist such as atropine in the eye of a patient.

The present disclosure recognizes that muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people. The present disclosure also recognizes the effects of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) on reduction of axial elongation and myopia in visually impaired chick eyes, and on ocular growth and muscarinic cholinergic receptors in young rhesus monkeys.

In addition, the present disclosure recognizes that systemic absorption of muscarinic antagonist (e.g. atropine) sometimes leads to undesirable side effect, and that localized delivery of muscarinic antagonist (e.g. atropine or its phar-

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maceutically acceptable salts) reduces or prevents the aforementioned systemic exposure.

Further, the present disclosure recognizes that some liquid muscarinic antagonist (e.g. atropine) compositions are formulated at a relatively lower pH range (e.g. less than 4.5) for stability of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). For some individuals, the lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye, which is prevented or alleviated by formulating muscarinic antagonist (e.g. atropine) compositions at higher pH ranges. For some individuals, the lower pH in some instances elicits a tear response which reduces the absorption of the drug in the eye and therefore the effectiveness.

Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present stability challenges that are less so in higher concentrations (e.g. 0.1-1%). Without wishing to be bound by any particular theory, it is contemplated that the some muscarinic antagonist (e.g. atropine) contributes to the stability of an ophthalmic composition, such as an aqueous solution. For example, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the pH or pD of the ophthalmic composition, such as with the muscarinic antagonist acting as a buffering agent. Furthermore, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the interaction between the muscarinic antagonist and other ingredients of the ophthalmic composition, which in turn affects the stability of the ophthalmic composition.

Finally, the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions. In some cases, the deuterated water is a weak acid as compared to H₂O, as such deuterated water comprises a lower concentration of the reactive species (e.g., —OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H₂O. In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

Myopia, axial elongation of the eye, affects a large proportion of the population. The onset of myopia is generally during the grade school years and progresses until growth of the eye is completed. The present disclosure recognizes the importance of compositions and treatments for preventing or arresting the development of myopia, especially compositions and treatments that allow convenient administration, reduce potential side effects, has suitable stability, and/or provide relatively consistent therapeutic effects.

Ophthalmic Muscarinic Antagonist Composition

Provided herein is an ophthalmic composition containing low concentrations of an ophthalmic agent. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. In some instances, the ophthalmic agent is a muscarinic antagonist.

Provided herein is an ophthalmic composition containing low concentrations of a muscarinic antagonist. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of a muscarinic

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antagonist for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the muscarinic antagonist is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the ophthalmic composition comprise a muscarinic antagonist selected from atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, or homatropine.

In some embodiments, the ophthalmic composition comprise two or more muscarinic antagonists in which the two or more muscarinic antagonists comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or any combination thereof.

In some embodiments, the ophthalmic composition comprises one or more muscarinic antagonist in combination with one or more sympathetic agonists. In some embodiments, the sympathetic agonist is selected from phenylephrine or hydroxyamphetamine. In some embodiments, the ophthalmic composition comprises one or more muscarinic antagonist: atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combination with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

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Provided herein is an ophthalmic composition containing low concentrations of atropine or its pharmaceutically acceptable salts. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of atropine or its pharmaceutically acceptable salts for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

Provided herein is an ophthalmic composition containing low concentrations of atropine sulfate. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of atropine sulfate for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

The present disclosure further recognizes that the clinical use of atropine as a therapy has been limited due to its ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation. Without wishing to be bound by any particular theory, it is contemplated that the limited use of atropine against myopia development, include its ocular side effects, is attributable to the concentration of atropine used in known ophthalmic formulations (e.g. 1 wt % or higher).

The present disclosure further recognizes the challenges present in formulation of compositions that contain low concentrations, especially very low concentrations (e.g. from about 0.001 wt % to about 0.5 wt %), of ophthalmic agents, such as muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). In particular, pharmaceutical compositions with ophthalmic agent at such low concentrations are difficult to maintain dose-to-dose uniformity in term of ophthalmic agent content and/or distribution.

In some aspects, described herein are formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water. In some aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent. In additional aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water has a lowered buffering capacity. In such instances, the lowered buffering capacity of the ophthalmic formulations or solutions when administered into the eye allows the ophthalmic formulation or solution to reach physiological pH at a faster rate than compared to an equivalent ophthalmic formulation or solution formulated in H₂O.

In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that does not have a dose-to-dose variation. In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

In other aspects, described herein include formulating the ophthalmic composition as an ophthalmic gel or an ophthalmic ointment. For example, some ophthalmic gel or an ophthalmic ointment described herein allows desirable dose-to-dose uniformity, reduced or limited systemic exposure, or combinations thereof.

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Ophthalmic Solution Muscarinic Antagonist Composition
Disclosed herein, in certain embodiments, is an ophthalmic composition formulated as an aqueous solution. In some embodiments, the ophthalmic composition comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water. As used herein, deuterated water refers to D₂O, DHO, heavy water, and/or deuterium oxide.

[illegible]

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nist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 98% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 99% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition.

[illegible]

In some embodiments, the extended period of time is at least 1 week. In some embodiments, the extended period of time is at least 2 weeks. In some embodiments, the extended period of time is at least 3 weeks. In some embodiments, the extended period of time is at least 1 month. In some embodiments, the extended period of time is at least 2 months. In some embodiments, the extended period of time is at least 3 months. In some embodiments, the extended period of time is at least 4 months. In some embodiments, the extended period of time is at least 5 months. In some embodiments, the extended period of time is at least 6 months. In some embodiments, the extended period of time is at least 7 months. In some embodiments, the extended period of time is at least 8 months. In some embodiments, the extended period of time is at least 9 months. In some

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embodiments, the extended period of time is at least 10 months. In some embodiments, the extended period of time is at least 11 months. In some embodiments, the extended period of time is at least 12 months (i.e. 1 year). In some embodiments, the extended period of time is at least 18 months (i.e. 1.5 years). In some embodiments, the extended period of time is at least 24 months (i.e. 2 years). In some embodiments, the extended period of time is at least 36 months (i.e. 3 years). In some embodiments, the extended period of time is at least 3 years. In some embodiments, the extended period of time is at least 5 years, or more.

In some embodiments, the temperature of the storage condition is between about 20° C. and about 70° C. In some embodiments, the temperature of the storage condition is between about 25° C. and about 65° C., about 30° C. and about 60° C., about 35° C. and about 55° C., or about 40° C. and about 50° C. In some embodiments, the temperature of the storage condition is about 25° C. In some embodiments, the temperature of the storage condition is about 40° C. In some embodiments, the temperature of the storage condition is about 60° C.

In some embodiments, the relative humidity of the storage condition is between about 50% and about 80%, or between about 60% and about 75%. In some embodiments, the relative humidity of the storage condition is about 60%. In some embodiments, the relative humidity of the storage condition is about 75%.

In some embodiments, the composition comprises less than 60% of H₂O. In some embodiments, the composition comprises less than 55% of H₂O. In some embodiments, the composition comprises less than 50% of H₂O. In some embodiments, the composition comprises less than 45% of H₂O. In some embodiments, the composition comprises less than 40% of H₂O. In some embodiments, the composition comprises less than 35% of H₂O. In some embodiments, the composition comprises less than 30% of H₂O. In some embodiments, the composition comprises less than 25% of H₂O. In some embodiments, the composition comprises less than 20% of H₂O. In some embodiments, the composition comprises less than 15% of H₂O. In some embodiments, the composition comprises less than 10% of H₂O.

In some embodiments, the composition comprises from less than 5% of H₂O to 0% of H₂O. In some embodiments, the composition comprises less than 5% of H₂O. In some embodiments, the composition comprises less than 4.5% of H₂O. In some embodiments, the composition comprises less than 4% of H₂O. In some embodiments, the composition comprises less than 3.5% of H₂O. In some embodiments, the composition comprises less than 3% of H₂O. In some embodiments, the composition comprises less than 2.5% of H₂O. In some embodiments, the composition comprises less than 2% of H₂O. In some embodiments, the composition comprises less than 1.5% of H₂O. In some embodiments, the composition comprises less than 1% of H₂O. In some embodiments, the composition comprises less than 0.5% of H₂O. In some embodiments, the composition comprises less than 0.4% of H₂O. In some embodiments, the composition comprises less than 0.3% of H₂O. In some embodiments, the composition comprises less than 0.2% of H₂O. In some embodiments, the composition comprises less than 0.1% of H₂O. In some embodiments, the composition comprises 0% of H₂O.

In some embodiments, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than

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about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments, the composition has a pD of less than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4.

In some embodiments, the composition comprising deuterated water has a lowered buffering capacity than an equivalent composition comprising H₂O. As described elsewhere herein, in some embodiments, the lowered buffering capacity allows the composition comprising deuterated water to normalize to physiological pH at a faster rate than a composition comprising H₂O. In some embodiments, the lowered buffering capacity allows the composition to induce less tear reflex than an equivalent composition comprising H₂O.

In some instances, the composition comprising deuterated water stabilizes muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a

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more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid.

In some embodiments, the primary degradant is an early eluting related substance at RRT of 0.87-0.89 according to the UPLC method described herein (Table 10). In some instances, the early eluting related substance is referred to as RRT 0.87-0.89. In some embodiments, the primary degradant is RRT 0.87-0.89.

In some embodiments, the composition does not stabilize singlet oxygen upon irradiation with UV. In some cases, one or more of muscarinic antagonists described herein does not extend singlet oxygen lifetime. In some cases, one or more of muscarinic antagonists described herein is a radical scavenger, which quenches photogenerated singlet oxygen species within the composition. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, homatropine, scopolamine or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine or atropine sulfate. In some instances, a composition comprising atropine or atropine sulfate does not stabilize singlet oxygen upon

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irradiation with UV. In some instances, a composition comprising atropine or atropine sulfate quenches photogenerated singlet oxygen species present in the composition.

Ophthalmic Muscarinic Antagonist Concentration

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.050%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate. As described herein, the ophthalmic agent includes optically pure stereoisomers, optically enriched stereoisomers, and a racemic mixture of stereoisomers. For example, some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a racemic mixture of D- and L-isomers; and some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is optically enriched in favor of the more ophthalmically active L-isomer.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.045%, between about 0.005% to about 0.045%, between about 0.010% to about 0.045%, between about 0.015% to about 0.045%, between about 0.020% to about 0.045%, between about 0.025% to about 0.045%, between about 0.030% to about 0.045%, between about 0.035% to about 0.045%, or between about 0.040% to about 0.045% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.040%, between about 0.005% to about 0.040%, between about 0.010% to about 0.040%, between about 0.015% to about 0.040%, between about 0.020% to about 0.040%, between about 0.025% to about 0.040%, between about 0.030% to about 0.040%, between about 0.035% to about 0.040% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic

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agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some

embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate. In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.035%, between about 0.005% to about 0.035%, between about 0.010% to about 0.035%, between about 0.015% to about 0.035%, between about 0.020% to about 0.035%, between about 0.025% to about 0.035%, or between about 0.030% to about 0.035% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.030%, between about 0.005% to about 0.030%, between about 0.010% to about 0.030%, between about 0.015% to about 0.030%, between about 0.020% to about 0.030%, or between about 0.025% to about 0.030% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.025%, between about 0.005% to about 0.025%, between about 0.010% to about 0.025%, between about 0.015% to about 0.025%, or between about 0.020% to about 0.025% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.020%, between about 0.005% to about 0.020%, between about 0.010% to about 0.020%, or between about 0.015% to about 0.020% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In

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some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.015%, between about 0.005% to about 0.015%, or between about 0.010% to about 0.015% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.010%, between about 0.005% to about 0.010%, or between about 0.008% to about 0.010% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

Without wishing to be bound by any particular theory, it is contemplated herein that the low concentration of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate) in the disclosed ophthalmic composition provides sufficient and consistent therapeutic benefits to an individual in need thereof, while reducing or avoiding the ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation that are associated with ophthalmic formulations containing higher concentrations of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate).

Aqueous Solution Stability

In some embodiments, the composition described herein comprises a buffer. In some embodiments, a buffer is

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selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof. In some embodiments, the composition described herein comprises buffer comprising deuterated water. In some embodiments, a deuterated buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof, formulated in deuterated water.

In some instances, borates include boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. In some cases, borates include boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

As used herein, the term polyol includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. In some embodiments, the polyols is linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. In some instances, examples of polyol include: sugars, sugar alcohols, sugar acids and uronic acids. In some cases, polyols include, but are not limited to: mannitol, glycerin, xylitol and sorbitol.

In some embodiments, phosphate buffering agents include phosphoric acid; alkali metal phosphates such as disodium hydrogen phosphate, sodium dihydrogen phosphate, trisodium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, and tripotassium phosphate; alkaline earth metal phosphates such as calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, monomagnesium phosphate, dimagnesium phosphate (magnesium hydrogen phosphate), and trimagnesium phosphate; ammonium phosphates such as diammonium hydrogen phosphate and ammonium dihydrogen phosphate; or a combination thereof. In some instances, the phosphate buffering agent is an anhydride. In some instances, the phosphate buffering agent is a hydrate.

In some embodiments, borate-polyol complexes include those described in U.S. Pat. No. 6,503,497. In some instances, the borate-polyol complexes comprise borates in an amount of from about 0.01 to about 2.0% w/v, and one or more polyols in an amount of from about 0.01% to about 5.0% w/v.

In some cases, citrate buffering agents include citric acid and sodium citrate.

In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

In some cases, organic buffering agents include Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), N-(2-Acetamido)iminodiacetic acid, N-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-N,N'-bis(2-ethanesulfonic acid (PIPES), N-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β -Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), cholamine chloride, 3-(N-morpholino)propanesulfonic acid (MOPS), N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 2-[(2-Hydroxy-1,1-bis(hydroxymethyl)ethyl)amino]ethanesulfonic acid (TES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 3-(N,N-Bis[2-hydroxy-

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ethyl]amino)-2-hydroxypropanesulfonic acid (DIPSO), acetamidoglycine, 3-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propanyl]amino]-2-hydroxy-1-propanesulfonic acid (TAPSO), piperazine-1,4-bis (2-hydroxypropanesulphonic acid) (POPSO), 4-(2-hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate (HEPPSO), 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid (HEPPS), tricine, glycineamide, bicine or N-tris(hydroxymethyl) methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; and diethanolamine (DEA).

In some cases, amino acid buffering agents include taurine, aspartic acid and its salts (e.g., potassium salts, etc), E-aminocaproic acid, and the like.

In some instances, the composition described herein further comprises a tonicity adjusting agent. Tonicity adjusting agent is an agent introduced into a preparation such as an ophthalmic composition to reduce local irritation by preventing osmotic shock at the site of application. In some instances, buffer solution and/or a pD adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pD are considered as tonicity adjusting agents. In some cases, tonicity adjusting agents include various salts, such as halide salts of a monovalent cation. In some cases, tonicity adjusting agents include mannitol, sorbitol, dextrose, sucrose, urea, and glycerin. In some instances, suitable tonicity adjusters comprise sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.5% and about 2.0%. In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.7% and about 1.8%, about 0.8% and about 1.5%, or about 1% and about 1.3%. In some instances, the concentration of the tonicity adjusting agent is about 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, or 1.9%. In some cases, the percentage is a weight percentage.

In some cases, the composition described herein further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent used is an acid or a base. In some embodiments, the base is oxides, hydroxides, carbonates, bicarbonates and the likes. In some instances, the oxides are metal oxides such as calcium oxide, magnesium oxide and the likes; hydroxides are of alkali metals and alkaline earth metals such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the likes or their deuterated equivalents, and carbonates are sodium carbonate, sodium bicarbonates, potassium bicarbonates and the likes. In some instances, the acid is mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric acid and the likes or their deuterated equivalents. In some instances, the pD adjusting agent includes, but is not limited to, acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agent comprises DCl and NaOD.

In some instances, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments,

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about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

As described elsewhere herein, in some instances, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., —OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., —OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the presence of deuterated water shifts the pKa of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quaternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

In some instances, the composition described herein further comprises a preservative. In some cases, a preservative is added at a concentration to a composition described herein to prevent the growth of or to destroy a microorganism introduced into the composition. In some instances, micro-

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organisms refer to bacteria (e.g. *Proteus mirabilis*, *Serratia marcescens*), virus (e.g. Herpes simplex virus, herpes zoster virus), fungus (e.g. fungi from the genus *Fusarium*), yeast (e.g. *Candida albicans*), parasites (e.g. *Plasmodium* spp., *Gnathostoma* spp.), protozoan (e.g. *Giardia lamblia*), nematodes (e.g. *Onchocercus volvulus*), worm (e.g. *Dirofilaria immitis*), and/or amoeba (e.g. *Acanthamoeba*).

In some instances, the concentration of the preservative is between about 0.0001% and about 1%, about 0.001% and about 0.8%, about 0.004% and about 0.5%, about 0.008% and about 0.1%, and about 0.01% and about 0.08%. In some cases, the concentration of the preservatives is about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.008%, 0.009%, 0.009%, 0.01%, 0.015%, 0.02%, 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9% or 1.0%.

In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia (Alcon), polyquaternium-1, chlorobutanol, edetate disodium, and polyhexamethylene biguanide.

In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the material of the plastic container comprises high density polyethylene (HDPE), low density polyethylene (LDPE), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polypropylene (PP), polystyrene (PS), fluorine treated HDPE, post-consumer resin (PCR), K-resine (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the composition stored in a plastic container has a pD of between about 4 and about 8, about 4.5 and about 7.9, or about 4.9 and about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.6. In some

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embodiments, the composition stored in a plastic container has a pD of less than about 5.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.

In some embodiments, the composition stored in a plastic container has a potency of at least 70% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 75% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 99% after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25° C., about 40° C., or about 60° C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

In some embodiments, the composition stored in a plastic container has a potency of at least 80% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 85% at a temperature of about 25°

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C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 90% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 93% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 95% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 97% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 98% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 99% at a temperature of about 25° C., about 40° C., or about 60° C.

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In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant

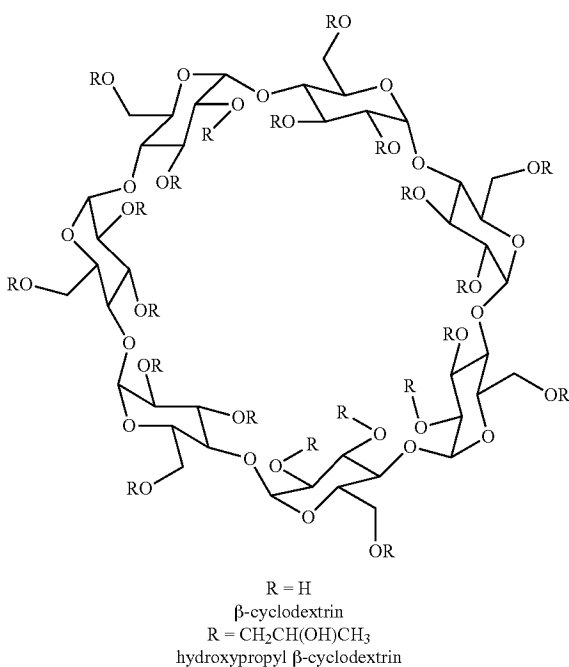
In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months,

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the aqueous solution is stored in the presence of light. In some instances, the aqueous solution is stable in the presence of light.

In a specific embodiment, the ophthalmically acceptable formulations alternatively comprise a cyclodextrin. Cyclodextrins are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, referred to as α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin respectively. Cyclodextrins have a hydrophilic exterior, which enhances water-soluble, and a hydrophobic interior which forms a cavity. In an aqueous environment, hydrophobic portions of other molecules often enter the hydrophobic cavity of cyclodextrin to form inclusion compounds. Additionally, cyclodextrins are also capable of other types of nonbonding interactions with molecules that are not inside the hydrophobic cavity. Cyclodextrins have three free hydroxyl groups for each glucopyranose unit, or 18 hydroxyl groups on α -cyclodextrin, 21 hydroxyl groups on β -cyclodextrin, and 24 hydroxyl groups on γ -cyclodextrin. In some embodiments, one or more of these hydroxyl groups are reacted with any of a number of reagents to form a large variety of cyclodextrin derivatives, including hydroxypropyl ethers, sulfonates, and sulfoalkylethers. Shown below is the structure of β -cyclodextrin and the hydroxypropyl- β -cyclodextrin (HP β CD).



In some embodiments, the use of cyclodextrins in the pharmaceutical compositions described herein improves the solubility of the drug. Inclusion compounds are involved in many cases of enhanced solubility; however other interactions between cyclodextrins and insoluble compounds also improves solubility. Hydroxypropyl- β -cyclodextrin (HP β CD) is commercially available as a pyrogen free product. It is a nonhygroscopic white powder that readily dissolves in water. HP β CD is thermally stable and does not degrade at neutral pH. Thus, cyclodextrins improve the solubility of a therapeutic agent in a composition or formulation. Accordingly, in some embodiments, cyclodextrins are included to increase the solubility of the ophthalmically acceptable ophthalmic agents within the formulations

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described herein. In other embodiments, cyclodextrins in addition serve as controlled release excipients within the formulations described herein.

By way of example only, cyclodextrin derivatives for use include α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxyethyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, sulfated β -cyclodextrin, sulfated α -cyclodextrin, sulfobutyl ether β -cyclodextrin.

The concentration of the cyclodextrin used in the compositions and methods disclosed herein varies according to the physiochemical properties, pharmacokinetic properties, side effect or adverse events, formulation considerations, or other factors associated with the therapeutically ophthalmic agent, or a salt or prodrug thereof, or with the properties of other excipients in the composition. Thus, in certain circumstances, the concentration or amount of cyclodextrin used in accordance with the compositions and methods disclosed herein will vary, depending on the need. When used, the amount of cyclodextrins needed to increase solubility of the ophthalmic agent and/or function as a controlled release excipient in any of the formulations described herein is selected using the principles, examples, and teachings described herein.

Other stabilizers that are useful in the ophthalmically acceptable formulations disclosed herein include, for example, fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinyl pyrrolidones, polyvinyl ethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof. In some embodiments, amide analogues of stabilizers are also used. In further embodiments, the chosen stabilizer changes the hydrophobicity of the formulation, improves the mixing of various components in the formulation, controls the moisture level in the formula, or controls the mobility of the phase.

In other embodiments, stabilizers are present in sufficient amounts to inhibit the degradation of the ophthalmic agent. Examples of such stabilizing agents, include, but are not limited to: glycerol, methionine, monothioglycerol, EDTA, ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate and other heparinoids, divalent cations such as magnesium and zinc, or combinations thereof.

Additional useful stabilization agents for ophthalmically acceptable formulations include one or more anti-aggregation additives to enhance stability of ophthalmic formulations by reducing the rate of protein aggregation. The anti-aggregation additive selected depends upon the nature of the conditions to which the ophthalmic agents, for example a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), are exposed. For example, certain formulations undergoing agitation and thermal stress require a different anti-aggregation additive than a formulation undergoing lyophilization and reconstitution. Useful anti-aggregation additives include, by way of example only, urea, guanidinium chloride, simple amino acids such as glycine or arginine, sugars, polyalcohols, polysorbates, polymers such as polyethylene glycol and dextrans, alkyl saccharides, such as alkyl glycoside, and surfactants.

Other useful formulations optionally include one or more ophthalmically acceptable antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid, methionine, sodium thiosulfate and sodium metabisulfite. In one embodiment, antioxidants are selected from metal chelating agents, thiol containing compounds and other general stabilizing agents.

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Still other useful compositions include one or more ophthalmically acceptable surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

In some embodiments, the ophthalmically acceptable pharmaceutical formulations described herein are stable with respect to compound degradation (e.g. less than 30% degradation, less than 25% degradation, less than 20% degradation, less than 15% degradation, less than 10% degradation, less than 8% degradation, less than 5% degradation, less than 3% degradation, less than 2% degradation, or less than 5% degradation) over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 3 months, at least about 4 months, at least about 5 months, or at least about 6 months under storage conditions (e.g. room temperature). In other embodiments, the formulations described herein are stable with respect to compound degradation over a period of at least about 1 week. Also described herein are formulations that are stable with respect to compound degradation over a period of at least about 1 month.

In other embodiments, an additional surfactant (co-surfactant) and/or buffering agent is combined with one or more of the pharmaceutically acceptable vehicles previously described herein so that the surfactant and/or buffering agent maintains the product at an optimal pD for stability. Suitable co-surfactants include, but are not limited to: a) natural and synthetic lipophilic agents, e.g., phospholipids, cholesterol, and cholesterol fatty acid esters and derivatives thereof; b) nonionic surfactants, which include for example, polyoxyethylene fatty alcohol esters, sorbitan fatty acid esters (Spans), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20) and other Tweens, sorbitan esters, glycerol esters, e.g., Myrj and glycerol triacetate (triacetin), polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, polysorbate 80, poloxamers, poloxamines, polyoxyethylene castor oil derivatives (e.g., Cremophor® RH40, Cremophor A25, Cremophor A20, Cremophor® EL) and other Cremophors, sulfosuccinates, alkyl sulphates (SLS); PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprate (Labrasol), PEG-4 glyceryl caprylate/caprate (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 444/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate; Brij® 700, ascorbyl-6-palmitate, stearylamine, sodium lauryl sulfate, polyoxyethyleneglycerol triiricinoleate, and any combinations or mixtures thereof; c) anionic surfactants include, but are not limited to, calcium carboxymethylcellulose, sodium carboxymethylcellulose, sodium sulfosuccinate, dioctyl, sodium alginate, alkyl polyoxyethylene sulfates, sodium lauryl sulfate, triethanolamine stearate, potassium laurate, bile salts, and any combinations or mixtures thereof; and d) cationic surfactants such as cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride.

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In a further embodiment, when one or more co-surfactants are utilized in the ophthalmically acceptable formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and is present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%.

In one embodiment, the surfactant has an HLB value of 0 to 20. In additional embodiments, the surfactant has an HLB value of 0 to 3, of 4 to 6, of 7 to 9, of 8 to 18, of 13 to 15, of 10 to 18.

pD

In some embodiments, the pD of a composition described herein is adjusted (e.g., by use of a buffer and/or a pD adjusting agent) to an ophthalmically compatible pD range of from about 4 to about 8, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition has a pD of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6.0 to about 7.0.

In some embodiments, useful formulations include one or more pD adjusting agents or buffering agents. Suitable pD adjusting agents or buffers include, but are not limited to acetate, bicarbonate, ammonium chloride, citrate, phosphate, deuterated forms of acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agents or buffers include deuterated hydrochloric acid (DCl), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).

In one embodiment, when one or more buffers are utilized in the formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and are present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%. In certain embodiments of the present disclosure, the amount of buffer included in the gel formulations are an amount such that the pD of the gel formulation does not interfere with the body's natural buffering system.

In one embodiment, diluents are also used to stabilize compounds because they provide a more stable environment. In some instances, salts dissolved in buffered solutions (which also provides pD control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

In some embodiments, the pD is calculated according to the formula disclosed in Glasoe et al., "Use of glass electrodes to measure acidities in deuterium oxide," J. Physical Chem. 64(1): 188-190 (1960). In some embodiment, the pD is calculated as $pD = pH^* + 0.4$, in which pH^* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).

In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4 and about 8, between about 4.5 and about 8, between about 4.9 and about 7.9, between about 5.4 and about 7.9, between about 5.9 and about 7.9, between about 6.4 and about 7.9, or between about 7.4 and about 7.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.5, between about 5.0 and about 7.5, between about 5.5 and about 7.5, between about 6.0 and about 7.5, or between about 7.0 and about 7.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.0, between about 5.0 and about 7.0, between about 5.5 and about 7.0, between

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aqueous composition has a pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 4. In some embodiments, the pD is an initial pD of the ophthalmic aqueous composition. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

In some instances, the ophthalmic aqueous composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5. In some embodiments, the ophthalmic

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about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

In some embodiments, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., —OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., —OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the presence of deuterated water shifts the pKa of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

In some embodiment, the ophthalmic gel or ointment composition described herein has a pD of about 4, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, or about 7.9.

In some embodiment, the pD of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization)) of ophthalmic formulations described herein. As used in the present disclosure, the term “aqueous composition” includes compositions that are based on D₂O.

In some embodiments, the pharmaceutical formulations described herein are stable with respect to pD over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months,

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at least about 12 months, at least about 18 months, at least about 24 months, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pD over a period of at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, or more.

Aqueous Solution Dose-to-Dose Uniformity

Typical ophthalmic aqueous solutions are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous solution includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous solution described herein is one drop of the aqueous solution composition from the eye drop bottle.

In some cases, described herein include ophthalmic aqueous compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand,

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even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

Aqueous Solution Viscosity

In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10 to about 50,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 100 to about 40,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 500 to about 30,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 1000 to about 20,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 2000 to about 10,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 4000 to about 8000 cps at about 20° C. and sheer rate of 1 s⁻¹.

In some embodiments, the ophthalmic aqueous formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 50,000 centipoise, between about 750 and 50,000 centipoise; between about 1000 and 50,000 centipoise; between about 1000 and 40,000 centipoise; between about 2000 and 30,000 centipoise; between about 3000 and 20,000 centipoise; between about 4000 and 10,000 centipoise, or between about 5000 and 8000 centipoise.

In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP.

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In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

Osmolarity

In some embodiments, a composition disclosed herein is formulated in order to not disrupt the ionic balance of the eye. In some embodiments, a composition disclosed herein has an ionic balance that is the same as or substantially the same as the eye. In some embodiments, a composition disclosed herein does not does not disrupt the ionic balance of the eye.

As used herein, “practical osmolarity/osmolality” or “deliverable osmolarity/osmolality” means the osmolarity/osmolality of a composition as determined by measuring the osmolarity/osmolality of the ophthalmic agent and all excipients except the gelling and/or the thickening agent (e.g., polyoxyethylene-polyoxypropylene copolymers, carboxymethylcellulose or the like). The practical osmolarity of a composition disclosed herein is measured by a suitable method, e.g., a freezing point depression method as described in Viegas et. al., Int. J. Pharm., 1998, 160, 157-162. In some instances, the practical osmolarity of a composition disclosed herein is measured by vapor pressure osmometry (e.g., vapor pressure depression method) that allows for determination of the osmolarity of a composition at higher temperatures. In some instances, vapor pressure depression method allows for determination of the osmolarity of a composition comprising a gelling agent (e.g., a thermoreversible polymer) at a higher temperature wherein the gelling agent is in the form of a gel.

In some embodiments, the osmolarity at a target site of action (e.g., the eye) is about the same as the delivered osmolarity of a composition described herein. In some embodiments, a composition described herein has a deliverable osmolarity of about 150 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 280 mOsm/L to about 370 mOsm/L or about 250 mOsm/L to about 320 mOsm/L.

The practical osmolality of an ophthalmic composition disclosed herein is from about 100 mOsm/kg to about 1000 mOsm/kg, from about 200 mOsm/kg to about 800 mOsm/kg, from about 250 mOsm/kg to about 500 mOsm/kg, or from about 250 mOsm/kg to about 320 mOsm/kg, or from about 250 mOsm/kg to about 350 mOsm/kg or from about 280 mOsm/kg to about 320 mOsm/kg. In some embodiments, a composition described herein has a practical osmolality of about 100 mOsm/L to about 1000 mOsm/L, about 200 mOsm/L to about 800 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 250 mOsm/L to about 320 mOsm/L, or about 280 mOsm/L to about 320 mOsm/L.

In some embodiments, suitable tonicity adjusting agents include, but are not limited to any pharmaceutically acceptable sugar, salt or any combinations or mixtures thereof, such as, but not limited to dextrose, glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. In some instances, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

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In some embodiment, the ophthalmic compositions described herein include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Sterility

In some embodiments, the compositions are sterilized. Included within the embodiments disclosed herein are means and processes for sterilization of a pharmaceutical composition disclosed herein for use in humans. The goal is to provide a safe pharmaceutical product, relatively free of infection causing micro-organisms. The U. S. Food and Drug Administration has provided regulatory guidance in the publication "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing" available at: <http://www.fda.gov/cder/guidance/5882fnl.htm>, which is incorporated herein by reference in its entirety.

As used herein, sterilization means a process used to destroy or remove microorganisms that are present in a product or packaging. Any suitable method available for sterilization of objects and compositions is used. Available methods for the inactivation of microorganisms include, but are not limited to, the application of extreme heat, lethal chemicals, or gamma radiation. In some embodiments, a process for the preparation of an ophthalmic formulation comprises subjecting the formulation to a sterilization method selected from heat sterilization, chemical sterilization, radiation sterilization or filtration sterilization. The method used depends largely upon the nature of the device or composition to be sterilized. Detailed descriptions of many methods of sterilization are given in Chapter 40 of Remington: The Science and Practice of Pharmacy published by Lippincott, Williams & Wilkins, and is incorporated by reference with respect to this subject matter.

Filtration

Filtration sterilization is a method used to remove but not destroy microorganisms from solutions. Membrane filters are used to filter heat-sensitive solutions. Such filters are thin, strong, homogenous polymers of mixed cellulosic esters (MCE), polyvinylidene fluoride (PVF; also known as PVDF), or polytetrafluoroethylene (PTFE) and have pore sizes ranging from 0.1 to 0.22 μm . Solutions of various characteristics are optionally filtered using different filter membranes. For example, PVF and PTFE membranes are well suited to filtering organic solvents while aqueous solutions are filtered through PVF or MCE membranes. Filter apparatus are available for use on many scales ranging from the single point-of-use disposable filter attached to a syringe up to commercial scale filters for use in manufacturing plants. The membrane filters are sterilized by autoclave or chemical sterilization. Validation of membrane filtration systems is performed following standardized protocols (Microbiological Evaluation of Filters for Sterilizing Liquids, Vol 4, No. 3. Washington, D.C.: Health Industry Manufacturers Association, 1981) and involve challenging the membrane filter with a known quantity (ca. $10^7/\text{cm}^2$) of unusually small microorganisms, such as *Brevundimonas diminuta* (ATCC 19146).

Pharmaceutical compositions are optionally sterilized by passing through membrane filters. Formulations comprising nanoparticles (U.S. Pat. No. 6,139,870) or multilamellar vesicles (Richard et al., International Journal of Pharmaceu-

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tics (2006), 312(1-2):144-50) are amenable to sterilization by filtration through 0.22 μm filters without destroying their organized structure.

In some embodiments, the methods disclosed herein comprise sterilizing the formulation (or components thereof) by means of filtration sterilization. In ophthalmic gel compositions that includes thermosetting polymers, filtration is carried out below (e.g. about 5° C.) the gel temperature (Tgel) of a formulation described herein and with viscosity that allows for filtration in a reasonable time using a peristaltic pump (e.g. below a theoretical value of 100 cP).

Accordingly, provided herein are methods for sterilization of ophthalmic formulations that prevent degradation of polymeric components (e.g., thermosetting and/or other viscosity enhancing agents) and/or the ophthalmic agent during the process of sterilization. In some embodiments, degradation of the ophthalmic agent (e.g., a muscarinic antagonist such as atropine or atropine sulfate) is reduced or eliminated through the use of specific pD ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pD range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation. Sterilization

One advantage of radiation sterilization is the ability to sterilize many types of products without heat degradation or other damage. The radiation commonly employed is beta radiation or alternatively, gamma radiation from a ^{60}Co source. The penetrating ability of gamma radiation allows its use in the sterilization of many product types, including solutions, compositions and heterogeneous mixtures. The germicidal effects of irradiation arise from the interaction of gamma radiation with biological macromolecules. This interaction generates charged species and free-radicals. Subsequent chemical reactions, such as rearrangements and cross-linking processes, result in the loss of normal function for these biological macromolecules. The formulations described herein are also optionally sterilized using beta irradiation.

Sterilization by Heat

Many methods are available for sterilization by the application of high heat. One method is through the use of a saturated steam autoclave. In this method, saturated steam at a temperature of at least 121° C. is allowed to contact the object to be sterilized. The transfer of heat is either directly to the microorganism, in the case of an object to be sterilized, or indirectly to the microorganism by heating the bulk of an aqueous solution to be sterilized. This method is widely practiced as it allows flexibility, safety and economy in the sterilization process.

Microorganisms

In some embodiments, the compositions are substantially free of microorganisms. Acceptable bioburden or sterility levels are based on applicable standards that define therapeutically acceptable compositions, including but not lim-

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ited to United States Pharmacopeia Chapters <111> et seq. For example, acceptable sterility (e.g., bioburden) levels include about 10 colony forming units (cfu) per gram of formulation, about 50 cfu per gram of formulation, about 100 cfu per gram of formulation, about 500 cfu per gram of formulation or about 1000 cfu per gram of formulation. In some embodiments, acceptable bioburden levels or sterility for formulations include less than 10 cfu/mL, less than 50 cfu/mL, less than 500 cfu/mL or less than 1000 cfu/mL microbial agents. In addition, acceptable bioburden levels or sterility include the exclusion of specified objectionable microbiological agents. By way of example, specified objectionable microbiological agents include but are not limited to *Escherichia coli* (*E. coli*), *Salmonella* sp., *Pseudomonas aeruginosa* (*P. aeruginosa*) and/or other specific microbial agents.

An important component of the sterility assurance quality control, quality assurance and validation process is the method of sterility testing. Sterility testing, by way of example only, is performed by two methods. The first is direct inoculation wherein a sample of the composition to be tested is added to growth medium and incubated for a period of time up to 21 days. Turbidity of the growth medium indicates contamination. Drawbacks to this method include the small sampling size of bulk materials which reduces sensitivity, and detection of microorganism growth based on a visual observation. An alternative method is membrane filtration sterility testing. In this method, a volume of product is passed through a small membrane filter paper. The filter paper is then placed into media to promote the growth of microorganisms. This method has the advantage of greater sensitivity as the entire bulk product is sampled. The commercially available Millipore Steritest sterility testing system is optionally used for determinations by membrane filtration sterility testing. For the filtration testing of creams or ointments Steritest filter system No. TLHVS210 are used. For the filtration testing of emulsions or viscous products Steritest filter system No. TLAREM210 or TDA-REM210 are used. For the filtration testing of pre-filled syringes Steritest filter system No. TTHASY210 are used. For the filtration testing of material dispensed as an aerosol or foam Steritest filter system No. TTHVA210 are used. For the filtration testing of soluble powders in ampoules or vials Steritest filter system No. TTHADA210 or TTHADV210 are used.

Testing for *E. coli* and *Salmonella* includes the use of lactose broths incubated at 30-35° C. for 24-72 hours, incubation in MacConkey and/or EMB agars for 18-24 hours, and/or the use of Rappaport medium. Testing for the detection of *P. aeruginosa* includes the use of NAC agar. United States Pharmacopeia Chapter <62> further enumerates testing procedures for specified objectionable microorganisms.

In certain embodiments, the ophthalmic formulation described herein has less than about 60 colony forming units (CFU), less than about 50 colony forming units, less than about 40 colony forming units, or less than about 30 colony forming units of microbial agents per gram of formulation. In certain embodiments, the ophthalmic formulations described herein are formulated to be isotonic with the eye.

Endotoxins

An additional aspect of the sterilization process is the removal of by-products from the killing of microorganisms (hereinafter, "Product"). The process of depyrogenation removes pyrogens from the sample. Pyrogens are endotoxins or exotoxins which induce an immune response. An example of an endotoxin is the lipopolysaccharide (LPS)

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molecule found in the cell wall of gram-negative bacteria. While sterilization procedures such as autoclaving or treatment with ethylene oxide kill the bacteria, the LPS residue induces a proinflammatory immune response, such as septic shock. Because the molecular size of endotoxins varies widely, the presence of endotoxins is expressed in "endotoxin units" (EU). One EU is equivalent to 100 picograms of *E. coli* LPS. In some cases, humans develop a response to as little as 5 EU/kg of body weight. The bioburden (e.g., microbial limit) and/or sterility (e.g., endotoxin level) is expressed in any units as recognized in the art. In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g., <4 EU/kg of body weight of a subject) when compared to conventionally acceptable endotoxin levels (e.g., 5 EU/kg of body weight of a subject). In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of body weight of a subject. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 2 EU/kg of body weight of a subject.

In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of formulation. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of formulation. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of formulation. In some embodiments, the ophthalmic formulation has less than about 5 EU/kg Product. In other embodiments, the ophthalmic formulation has less than about 1 EU/kg Product. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/kg Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/g of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/g of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/g of unit or Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/mg of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/mg of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/mg of unit or Product. In certain embodiments, ophthalmic formulations described herein contain from about 1 to about 5 EU/mL of formulation. In certain embodiments, ophthalmic formulations described herein contain from about 2 to about 5 EU/mL of formulation, from about 3 to about 5 EU/mL of formulation, or from about 4 to about 5 EU/mL of formulation.

In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g., <0.5 EU/mL of formulation) when compared to conventionally acceptable endotoxin levels (e.g., 0.5 EU/mL of formulation). In some embodiments, the ophthalmic formulation has less than about 0.5 EU/mL of formulation. In other embodiments, the ophthalmic formulation has less than about 0.4 EU/mL of formulation. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/mL of formulation.

Pyrogen detection, by way of example only, is performed by several methods. Suitable tests for sterility include tests described in United States Pharmacopoeia (USP)<71> Sterility Tests (23rd edition, 1995). The rabbit pyrogen test and the *Limulus* amoebocyte lysate test are both specified in the United States Pharmacopeia Chapters <85> and <151> (USP23/NF 18, Biological Tests, The United States Pharmacopoeial Convention, Rockville, Md., 1995). Alternative

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pyrogen assays have been developed based upon the monocyte activation-cytokine assay. Uniform cell lines suitable for quality control applications have been developed and have demonstrated the ability to detect pyrogenicity in samples that have passed the rabbit pyrogen test and the *Limulus* amoebocyte lysate test (Taktak et al, J. Pharm. Pharmacol. (1990), 43:578-82). In an additional embodiment, the ophthalmic formulation is subject to depyrogenation. In a further embodiment, the process for the manufacture of the ophthalmic formulation comprises testing the formulation for pyrogenicity. In certain embodiments, the formulations described herein are substantially free of pyrogens.

Ophthalmic Muscarinic Antagonist-Mucus Penetrating Particle (MPP) Composition

Mucus-penetrating particles (MPPs) are particles that rapidly traverse mucus (e.g. human mucus). In some cases, MPPs comprise of a nanoparticle with a particle size of between about 200 nm and 500 nm. In some instances, the nanoparticle is further coated with a mucus penetrating agent. In some instances, a composition described herein is formulated with MPPs for mucus penetration. In some instances, an ophthalmic agent composition described herein is formulated with MPPs for mucus penetration. In some instances, the ophthalmic agent is a muscarinic antagonist. In some instances, a muscarinic antagonist composition described herein is formulated with MPPs for mucus penetration. In some instances, a muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine. In some instances, a muscarinic antagonist is atropine or its pharmaceutically acceptable salt thereof. In some instances, a muscarinic antagonist is atropine sulfate. In some instances, an atropine composition described herein is formulated with MPPs for mucus penetration. In some instances, an atropine sulfate composition described herein is formulated with MPPs for mucus penetration. In a non-limiting example, the MPPs for use in the disclosed composition is obtained from Kala Pharmaceuticals, Inc. (100 Beaver Street #201, Waltham, Mass. 02453).

In some embodiments, the nanoparticle comprises of any suitable material, such as an organic material, an inorganic material, a polymer, or combinations thereof. In some instances, the nanoparticle comprises of inorganic material, such as for example, a metal (e.g., Ag, Au, Pt, Fe, Cr, Co, Ni, Cu, Zn, and other transition metals), a semiconductor (e.g., silicon, silicon compounds and alloys, cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide), or an insulator (e.g., ceramics such as silicon oxide). In some instances, the nanoparticle comprises organic materials such as a synthetic polymer and/or a natural polymer. Examples of synthetic polymers include non-degradable polymers such as polymethacrylate and degradable polymers such as polylactic acid, polyglycolic acid and copolymers thereof. Examples of natural polymers include hyaluronic acid, chitosan, and collagen.

In some embodiments, the nanoparticle is coated with a mucus penetrating agent. In some instances, the mucus penetrating agent comprises any suitable material, such as a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some instances, the mucus penetrat-

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ing agent is a polymer. In some instances, the polymer a synthetic polymer (i.e., a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (e.g., a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer is a diblock copolymer, a triblock copolymer, e.g., e.g., where one block is a hydrophobic polymer and another block is a hydrophilic polymer. In some embodiments, the polymer is charged or uncharged.

Additional examples of suitable polymers include, but are not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate), polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.

In some cases, an ophthalmic agent (e.g. a muscarinic antagonist such as atropine or atropine sulfate) is present in the MPP formulation at a concentration of between about 0.001 wt % and about 0.05 wt %, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable pro-drug or salt thereof, by weight of the composition. In some

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instances, additional agents such as buffers, pH adjusting agents, and/or preservatives are formulated in the MPP formulation.

In some instances, ophthalmic agent-MPP composition is formulated using any suitable method. In some embodiments, a milling process is used to reduce the size of a solid material to form particles in the micrometer to nanometer size range. In some cases, dry and wet milling processes such as jet milling, cryo-milling, ball milling, media milling, and homogenization are known and are used in methods described herein. Generally, in a wet milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. Dry milling is a process wherein the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. In a cryo-milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients under cooled temperatures.

In some embodiments, any suitable grinding medium is used for milling. In some embodiments, a ceramic and/or polymeric material and/or a metal is used. Examples of suitable materials include zirconium oxide, silicon carbide, silicon oxide, silicon nitride, zirconium silicate, yttrium oxide, glass, alumina, alpha-alumina, aluminum oxide, polystyrene, poly(methyl methacrylate), titanium, steel. In some cases, a grinding medium has any suitable size. For example, the grinding medium has an average diameter of at least about 0.1 mm, at least about 0.2 mm, at least about 0.5 mm, at least about 0.8 mm, at least about 1 mm, at least about 2 mm, or at least about 5 mm. In some cases, the grinding medium has an average diameter of less than or equal to about 5 mm, less than or equal to about 2 mm, less than or equal to about 1 mm, less than or equal to about 0.8 mm, less than or equal to about 0.5 mm, or less than or equal to about 0.2 mm. Combinations of the above-referenced ranges are also possible (e.g. an average diameter of at least about 0.5 millimeters and less than or equal to about 1 mm). Other ranges are also possible.

In some embodiments, any suitable solvent are used for milling. In some cases, the choice of solvent is depend on factors such as the solid material (e.g., a muscarinic antagonist such as atropine) being milled, the particular type of stabilizer/mucus penetrating agent being used (e.g., one that renders the particle mucus penetrating), the grinding material to be used, among other factors. In some cases, suitable solvents are ones that do not substantially dissolve the solid material or the grinding material, but dissolve the stabilizer/mucus penetrating agent to a suitable degree. Non-limiting examples of solvents include, but are not limited to, water, buffered solutions, other aqueous solutions, alcohols (e.g., ethanol, methanol, butanol), and mixtures thereof that optionally include other components such as pharmaceutical excipients, polymers, pharmaceutical agents, salts, preservative agents, viscosity modifiers, tonicity modifier, taste masking agents, antioxidants, pH modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent is used. In some cases, a pharmaceutical agent (e.g. a muscarinic antagonist such as atropine) has any suitable solubility in these or other solvents, such as a solubility in one or more of the ranges described above for aqueous solubility or for solubility in a coating solution.

In some instances, a MPP is a MPP as described in WO2013/166385. In some instances, a MPP is a MPP as described in Lai et al., "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," PNAS 104(5):1482-1487 (2007). In some instances, an ophthalmic

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agent-MPP composition is formulated using a method as described in WO2013/166385. In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in Lai et al., "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," PNAS 104(5):1482-1487 (2007). In some instances, the ophthalmic agent is a muscarinic antagonist such as atropine or atropine sulfate.

Muscarinic Antagonist-Ophthalmic Delivery Devices and Delivery System

In some embodiments, a muscarinic antagonist described herein is delivered to a target site by an ophthalmic delivery device. In some cases, the ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist comprises atropine or atropine sulfate.

In some embodiments, an ophthalmic delivery device comprises a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device. In some instances, a non-invasive delivery device comprises topical ophthalmic drug delivery device (TODD) or a contact lens. In some instances, the ophthalmic delivery device is a biodegradable ophthalmic delivery device. In other instances, the ophthalmic delivery device is a non-biodegradable ophthalmic delivery device. In some cases, the biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In other cases, the non-biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist.

In some instances, an ophthalmic delivery device comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In some cases, the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the ophthalmic delivery device, and is configured for a controlled sustained release of the muscarinic antagonist. In some instances, the ophthalmic delivery device is a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device.

Punctal Plug

A punctal plug or tear duct plug is an ocular device that in some cases is inserted into the tear duct (or puncta) of an eye. In some instances, a punctal plug is used for the delivery of an ophthalmic composition, for example, an ophthalmic composition described herein. In some cases, a punctal plug is used for the delivery of a muscarinic antagonist formulated in deuterated water. In additional cases, a punctal plug is used for the delivery of atrophic or atropine sulfate formulated in deuterated water.

In some instances, a punctal plug is used for controlled sustained release of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the period of controlled sustained release is, for example, up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 30, 45, 60 days or longer. In some instances, the period of controlled sustained release is, for example, up to 7 days. In some cases, the period of con-

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trolled sustained release is, for example, up to 14 days. In some cases, the period of controlled sustained release is, for example, up to 1 month.

In some embodiments, a punctal plug comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed within the punctal plug material, and is configured for a controlled sustained release of the muscarinic antagonist.

In some embodiments, a punctal plug described herein utilizes a diffusion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some instances, the configuration of the punctal plug is tubular with its cylindrical wall closed by transverse end walls to define a reservoir for the muscarinic antagonist (either in liquid or gel form). In some cases, at least the cylindrical wall is a membrane permeable by diffusion so that the muscarinic antagonist is released continuously at a controlled rate through the membrane into the tear fluid.

Exemplary materials for a permeable membrane for the diffusion mechanism include insoluble microporous materials of polycarbonates, polyvinyl chlorides, polyamides, copolymers of polyvinyl chloride and acrylonitrile, polysulfones, polyvinylidene fluorides, polyvinyl fluorides, polychloroethers, polyformaldehydes, acrylic resins, polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetates, polyethers, cellulose esters, porous rubbers, cross-linked poly(ethylene oxide), cross-linked polyvinyl pyrrolidone, cross-linked poly(vinyl alcohol) and polystyrenes.

In some embodiments, a punctal plug described herein utilizes an osmosis mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is tubular with domed end walls, and the device comprises a transverse impermeable elastic membrane dividing the tubular interior of the device into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. In some cases, a drug release aperture is included in the impermeable end wall of the device. When the device is placed in the aqueous environment of the eye water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

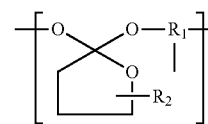
Examples of materials for an osmotic semi-permeable membrane include cellulose acetate and its derivatives, partial and completely hydrolyzed ethylene-vinyl acetate copolymers, highly plasticized polyvinyl chloride, homo- and copolymers of polyvinyl acetate, polyesters of acrylic acid and methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride; silicone polycarbonates, aromatic nitrogen-containing polymeric membranes, polymeric epoxides, copolymers of an alkylene oxide and alkyl glycidyl ether, polyurethanes, polyglycolic or polylactic acid and derivatives thereof, derivatives of polystyrene such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), ethylene-vinyl acetate copolymers.

In some embodiments, a punctal plug described herein utilizes a bioerosion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is rod-like being constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the device with tear

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fluid results in controlled sustained release of the drug by bioerosion of the matrix. In such cases, the drug is dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

Examples of bioerodible matrix materials include polyesters of the general formula —O—(W)—CO— and mixture thereof, wherein W is a lower alkylene of 1 to 7 carbons and may include a member selected from the group of alkenes of the formula $\text{—CH}_2\text{—}$, or $\text{—CH=CH}_2\text{—}$, and Y has a value such that the molecular weight of the polymer is from about 4,000 to 100,000. The polymers are polymerization-condensation products of monobasic hydroxy acid of the formula $\text{C}_n\text{H}_{2n}(\text{OH})\text{COOH}$ wherein n has a value of 1 to 7, preferably 1 or 2 and the acid is especially lactic acid or glycolic acid. Also included are copolymers derived from mixtures of these acids. Bioerodible materials also include poly(orthoesters). These materials have the following general formula:



wherein R_1 is an alkylene of 4 to 12 carbons, a cycloalkylene of 5 to 6 carbons substituted with an alkylene of 1 to 7 carbons and an alkyleneoxy of 1 to 7 carbons, and R_2 is a lower alkyl of 1 to 7 carbons.

Additional bioerodible matrix materials include: (1) Poly-anhydrides such as poly(p-carboxyphenoxy) alkyl (e.g. p-carboxyphenoxypropane) or polymeric fatty acid dimer (e.g. poly-dodecanedioic acid) compounds and further copolymers with sebacic acid, or phthalic acid such as disclosed in Chasin et al., Poly-anhydrides for Controlled Drug Delivery, *Biopharm.*, February 1988, 33-46; and Lee et al. (1988), The Use of Bioerodible Polymers and 5 fluorouracil in Glaucoma Filtration Surgery, *Invest. Ophthalmol. Vis. Sci.*, 29, 1692-1697; (2) Poly (alkyl-2-cyanoacrylates) such as poly (hexyl-2-cyanoacrylate) as described by Douglas et al. (1987). Nanoparticles in Drug Delivery. CRC Crit. Rev. Therap. Drug Carr. System., 3, 233-261; and (3) Polyamino acids such as copolymers of leucine and methyl glutamate.

In some cases, a punctal plug described herein comprises a solid non-erodible rod with pores. In some instances, the release of a muscarinic antagonist takes place via diffusion through the pores. In such instances, controlled release is further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

Examples of materials for use as non-erodible rods include polymers such as hydroxyethylmethacrylate and co-polymers with methacrylic acid, methylmethacrylate, N-vinyl 2-pyrrolidone, allyl methacrylate, ethylene glycol dimethacrylate, ethylene dimethacrylate, or 1,1,1 trimethylpropane trimethacrylate, and dimethyl diphenyl methyl-vinyl polysiloxane.

In some instances, the body of the plug is wholly or partially transparent or opaque. Optionally, the body includes a tint or pigment that makes the plug easier to see when it is placed in a punctum.

In some cases, the surface of the plug body is wholly or partially coated. In some cases, the coating provides one or more of lubriciousness to aid insertion, muco-adhesiveness to improve tissue compatibility, and texture to aid in anchor-

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ing the plug within the punctum. Examples of suitable coatings include, without limitation, gelatin, collagen, hydroxyethyl methacrylate, PVP, PEG, heparin, chondroitin sulphate, hyaluronic acid, synthetic and natural proteins, and polysaccharides, thiomers, thiolated derivatives of polyacrylic acid and chitosan, polyacrylic acid, carboxymethyl cellulose and the like and combinations thereof.

In some embodiments, a punctal plug described herein is a punctal plug described in U.S. Pat. No. 5,147,647; U.S. Publication No. 2012/0277694; or 2010/0256557.

In some instances, the size of the opening of the punctal plug is from about 0.05 mm to about 2.5 mm. In some instances, it is from about 0.1 mm to about 2.0 mm, or from about 0.15 mm to about 1 mm.

In some embodiments, the amount of a muscarinic antagonist (e.g., atropine or atropine sulfate) used in the plugs depends upon the muscarinic antagonist selected, the desired doses to be delivered via the punctal plug, the desired release rate, and the melting points of the muscarinic antagonist and muscarinic antagonist-containing material.

Scleral Patch or Scleral Ring

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a scleral patch or a scleral ring. In some instances, a scleral patch or a scleral ring is a biodegradable scleral patch or scleral ring. In other instances, a scleral patch or a scleral ring is a non-biodegradable scleral patch or scleral ring. In additional instances, a scleral patch or a scleral ring is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a scleral patch comprises a multi-layered patch in which one or more layer within the patch comprises a muscarinic antagonist described herein. In some cases, a scleral ring comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the scleral patch or the scleral ring.

Cul-De Sac Inserts

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a Cul-de sac insert. In some instances, the Cul-de sac insert comprises a single-layered device comprising muscarinic antagonist dispersed within the insert material, or multilayered, solid or semisolid consistency insert. In some instances, the Cul-de sac insert is a biodegradable insert. In other instances, the Cul-de sac insert is a non-biodegradable insert. In additional instances, a Cul-de sac insert is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some instances, a Cul-de sac insert comprises a membrane-bound ocular insert, which comprises of two outer layers of a copolymer such as ethylene-vinyl acetate copolymer (EVA) and an inner layer comprising a muscarinic antagonist. In some instances, the muscarinic antagonist within the inner layer is formulated as a gel or as a solution. An exemplary membrane-bound ocular insert is Ocuserts from Alza Corp.

In some cases, a Cul-de sac insert comprises an ocular film or sheath (mucoadhesive film or sheath or collagen shields), a coil, a polymer rod, HEMA hydrogel, or polysulfone capillary fiber. In some instances, a Cul-de sac insert comprises rod-shaped water soluble insert comprising of hydroxypropyl cellulose, a muscarinic antagonist, and one or more additional excipients. In some instances, the Cul-de

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sac insert comprising a rod-shaped water soluble insert is a biodegradable insert. An example comprises Lacrisert (Merck).

Subconjunctival/Episcleral Implant

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a subconjunctival/episcleral implant. In some instances, a subconjunctival/episcleral implant is a biodegradable implant. In other instances, a subconjunctival/episcleral implant is a non-biodegradable implant. In additional instances, a subconjunctival/episcleral implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a subconjunctival/episcleral implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the subconjunctival/episcleral implant. Exemplary subconjunctival/episcleral implants include LX201 (Lux Biosciences Inc.), an episcleral implant from 3T Ophthalmics, or a subconjunctival insert from Pfizer.

Intravitreal Implants

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through an intravitreal implant. In some instances, an intravitreal implant is a biodegradable implant. In other instances, an intravitreal implant is a non-biodegradable implant. In additional instances, an intravitreal implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, an intravitreal implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the intravitreal implant. Exemplary intravitreal implant comprises DuraserTM technology system (pSivida Corp.) (such as Vitrasert[®] and Retisert[®] from Bausch & Lomb Inc, and Iluvien[®] from Alimera sciences), NovadurTM technology system (such as Ozurdex[®] from Allergan), I-VationTM technology system (such as a delivery system developed from SurModics, Inc.), and NT-501 from Neurotech Pharmaceuticals.

Non-Invasive Delivery System

In some embodiments, a non-invasive delivery system comprises a topical ophthalmic agent delivery device. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device comprises a soft elastomer drug depot that floats atop the sclera under the eyelid. In some instances, the topical ophthalmic agent delivery device is a biodegradable delivery device. In other instances, the topical ophthalmic agent delivery device is a non-biodegradable delivery device. In some cases, the topical ophthalmic agent delivery device is impregnated with a muscarinic antagonist described herein. In other cases, a muscarinic antagonist is dispersed (e.g., uniformly) in the topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device is formulated for controlled sustained release of the muscarinic antagonist. In some instances, an exemplary delivery device is a topical ophthalmic drug delivery device (TODD) from Amorphex Therapeutics.

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In some embodiments, a non-invasive delivery system comprises a contact lens. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a contact lens. In some instances, the contact lens is impregnated with a muscarinic antagonist, for example, in which the muscarinic antagonist is dispersed, e.g., as colloidal structure, within the lens. In other instances, the contact lens is further combined with a muscarinic antagonist layer, and is configured for controlled sustained release to the eye. Exemplary polymers, e.g., hydrogel copolymers, for making a contact lens include at least one hydrophilic monomer and a crosslinking agent (a crosslinker being defined as a monomer having multiple polymerizable functionalities). Representative, hydrophilic monomers include: unsaturated carboxylic acids, such as methacrylic acid and acrylic acid; (meth)acrylic substituted alcohols, such as 2-hydroxyethylmethacrylate and 2-hydroxyethylacrylate; vinyl lactams, such as N-vinyl pyrrolidone; and (meth) acrylamides, such as methacrylamide and N,N-dimethylacrylamide. Typical crosslinking agents include polyvinyl, typically di- or tri-vinyl monomers, such as di- or tri(meth) acrylates of diethyleneglycol, triethyleneglycol, butyleneglycol and hexane-1,6-diol; and divinylbenzene. A specific example of a hydrogel-forming monomer mixture is polymacon, composed primarily of 2-hydroxyethylmethacrylate with a small amount of diethyleneglycol dimethacrylate as a crosslinking monomer. Optionally, the monomer mixture may include a silicone-containing monomer in order to form a silicone hydrogel copolymer. Examples of silicone-containing monomers include: monomers including a single activated unsaturated radical, such as methacryloxypropyl tris(trimethylsiloxy)silane, pentamethyldisiloxanyl methylmethacrylate, tris(trimethylsiloxy)methacryloxy propylsilane, methyltri(trimethylsiloxy)methacryloxyethyl silane, 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbamate, and 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbonate; and multifunctional ethylenically "end-capped" siloxane-containing monomers, especially difunctional monomers having two activated unsaturated radicals. A specific example of a silicone hydrogel-forming monomer mixture is balaficon, based on N-vinyl pyrrolidone and the aforementioned vinyl carbonate and carbamate monomers, disclosed in U.S. Pat. No. 5,260,000.

Ophthalmic Gel Muscarinic Antagonist Composition

Gels have been defined in various ways. For example, the United States Pharmacopoeia defines gels as semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels include a single-phase or a two-phase system. A single-phase gel consists of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Some single-phase gels are prepared from synthetic macromolecules (e.g., carbomer) or from natural gums, (e.g., tragacanth). In some embodiments, single-phase gels are generally aqueous, but will also be made using alcohols and oils. Two-phase gels consist of a network of small discrete particles.

In some embodiments, gels are also classified as being hydrophobic or hydrophilic. In certain embodiments, the base of a non-limiting example of a hydrophobic gel includes a liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, or aluminum or zinc soaps. In contrast, the base of a non-limiting example of a hydrophilic gel includes water, glycerol, or propylene glycol gelled with a suitable gelling agent (e.g., tragacanth, starch, cellulose derivatives, carboxyvinylpolymers, and magnesium-alumi-

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num silicates). In certain embodiments, the rheology of the compositions disclosed herein is pseudo plastic, plastic, thixotropic, or dilatant.

In some embodiments, the ophthalmic composition is an ophthalmic gel, and wherein the ophthalmically acceptable carrier comprises water and at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

In some embodiment, the ophthalmic gel composition described herein is a semi-solid or id in a gelled state before it is topically administered (e.g. at room temperature). For example, suitable viscosity-enhancing agents for such gels include by way of example only, gelling agents and suspending agents. In one embodiment, the enhanced viscosity formulation does not include a buffer. In other embodiments, the enhanced viscosity formulation includes a pharmaceutically acceptable buffer. Sodium chloride or other tonicity agents are optionally used to adjust tonicity, if necessary.

By way of example only, the ophthalmically acceptable viscosity agent includes hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate. Other viscosity enhancing agents compatible with the targeted ocular site include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), *ceratonia*, chitin, carboxymethylated chitosan, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthum gum, gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), Splenda® (dextrose, maltodextrin and sucralose) or combinations thereof. In specific embodiments, the viscosity-enhancing excipient is a combination of MCC and CMC. In another embodiment, the viscosity-enhancing agent is a combination of carboxymethylated chitosan, or chitin, and alginate. The combination of chitin and alginate with the ophthalmic agents disclosed herein acts as a controlled release formulation, restricting the diffusion of the ophthalmic agents from the formulation. Moreover, the combination of carboxymethylated chitosan and alginate is optionally used to assist in increasing the permeability of the ophthalmic agents in the eye.

In some embodiments is an enhanced viscosity formulation, comprising from about 0.1 mM and about 100 mM of an ophthalmic agent, a pharmaceutically acceptable viscosity agent, and water for injection, the concentration of the viscosity agent in the water being sufficient to provide an enhanced viscosity formulation with a final viscosity from about 100 to about 100,000 cP. In certain embodiments, the viscosity of the gel is in the range from about 100 to about 50,000 cP, about 100 cP to about 1,000 cP, about 500 cP to

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about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 50,000 cP, about 10,000 cP to about 500,000 cP, about 15,000 cP to about 1,000,000 cP. In other embodiments, when an even more viscous medium is desired, the biocompatible gel comprises at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 70%, at least about 75%, or even at least about 80% or so by weight of the ophthalmic agent. In highly concentrated samples, the biocompatible enhanced viscosity formulation comprises at least about 25%, at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 75%, at least about 85%, at least about 90% or at least about 95% or more by weight of the ophthalmic agent.

In one embodiment, the pharmaceutically acceptable enhanced viscosity ophthalmically acceptable formulation comprises at least one ophthalmic agent and at least one gelling agent. Suitable gelling agents for use in preparation of the gel formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum and any combinations or mixtures thereof. In some other embodiments, hydroxypropylmethylcellulose (Methocel®) is utilized as the gelling agent. In certain embodiments, the viscosity enhancing agents described herein are also utilized as the gelling agent for the gel formulations presented herein.

In some embodiments, the ophthalmic gel composition described herein is an in situ gel formulation. In some instances, the in situ gel formation is based on increased pre-corneal residence time of the ophthalmic composition which improves ocular bioavailability, corneal mucoadhesion, lysosomal interaction and ionic gelation, improved corneal absorption, thermal gelation, or a combination thereof. In some instances, the in situ gel formulation is activated by pH, temperature, ion, UV, or solvent exchange.

In some instances, the ophthalmic gel composition comprises a muscarinic antagonist and one or more gelling agents. In some instances, the gelling agent includes, but is not limited to, poloxamer (e.g. Poloxamer 407), tetronics, ethyl (hydroxyethyl) cellulose, cellulose acetate phthalate (CAP), carbopol (e.g. Carbopol 1342P NF, Carbopol 980 NF), alginates (e.g. low acetyl gellan gum (Gelrite®)), gellan, hyaluronic acid, pluronics (e.g. Pluronic F-127), chitosan, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), dextran, hydroxy propyl methyl cellulose (HPMC), hydroxyethylcellulose (HEC), methylcellulose (MC), thiolated xyloglucan, polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, xyloglucans, or combinations thereof.

In some instances, the in situ gel formation further comprises a permeation enhancer. In some instances, the permeation enhancer includes surfactants (e.g. non-ionic surfactants), benzalkonium chloride, EDTA, surface-active heteroglycosides, calcium chelators, hydroxyl propyl beta cyclodextrin (HP beta CD), bile salts, and the like.

In some embodiments, other gel formulations are useful depending upon the particular ophthalmic agent, other pharmaceutical agent or excipients/additives used, and as such are considered to fall within the scope of the present disclosure. For example, other commercially-available glycerin-based gels, glycerin-derived compounds, conjugated, or crosslinked gels, matrices, hydrogels, and polymers, as well

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as gelatins and their derivatives, alginates, and alginate-based gels, and even various native and synthetic hydrogel and hydrogel-derived compounds are all expected to be useful in the ophthalmic agent formulations described herein. In some embodiments, ophthalmically acceptable gels include, but are not limited to, alginate hydrogels SAF®-Gel (ConvaTec, Princeton, N.J.), Duoderm® Hydroactive Gel (ConvaTec), Nu-gel® (Johnson & Johnson Medical, Arlington, Tex.); Carrasyn® (V) Acemannan Hydrogel (Carrington Laboratories, Inc., Irving, Tex.); glycerin gels Elta® Hydrogel (Swiss-American Products, Inc., Dallas, Tex.) and K-Y® Sterile (Johnson & Johnson). In further embodiments, biodegradable biocompatible gels also represent compounds present in ophthalmically acceptable formulations disclosed and described herein.

In some embodiments, the viscosity-enhancing agent is a cellulose-based polymer selected from cellulose gum, alkylcellulose, hydroxyl-alkyl cellulose, hydroxyl-alkyl alkylcellulose, carboxy-alkyl cellulose, or combinations thereof. In some embodiments, the viscosity-enhancing agent is hydroxyl-alkyl alkylcellulose. In some embodiment, the viscosity-enhancing agent is hydroxypropyl methylcellulose.

In certain embodiments, the enhanced viscosity formulation is characterized by a phase transition between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42° C.). In some embodiments, the phase transition occurs at 1° C. below body temperature, at 2° C. below body temperature, at 3° C. below body temperature, at 4° C. below body temperature, at 6° C. below body temperature, at 8° C. below body temperature, or at 10° C. below body temperature. In some embodiments, the phase transition occurs at about 15° C. below body temperature, at about 20° C. below body temperature or at about 25° C. below body temperature. In specific embodiments, the gelation temperature (Tgel) of a formulation described herein is about 20° C., about 25° C., or about 30° C. In certain embodiments, the gelation temperature (Tgel) of a formulation described herein is about 35° C., or about 40° C. Included within the definition of body temperature is the body temperature of a healthy individual, or an unhealthy individual, including an individual with a fever (up to ~42° C.). In some embodiments, the pharmaceutical compositions described herein are liquids at about room temperature and are administered at or about room temperature.

Copolymers polyoxypropylene and polyoxyethylene (e.g. polyoxyethylene-polyoxypropylene triblock copolymers) form thermosetting gels when incorporated into aqueous solutions. These polymers have the ability to change from the liquid state to the gel state at temperatures close to body temperature, therefore allowing useful formulations that are applied to the targeted ocular site. The liquid state-to-gel state phase transition is dependent on the polymer concentration and the ingredients in the solution.

In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 15%, about 20%, about 25%, about 30%, about 35% or about 40% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24% or about 25% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 7.5% of the total

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weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 10% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 11% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 12% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 13% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 14% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 15% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 16% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 17% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 18% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 19% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 20% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 21% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 23% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 25% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 1%, about 5%, about 10%, or about 15% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, or about 5% of the total weight of the formulation.

In an alternative embodiment, the thermogel is a PEG-PLGA-PEG triblock copolymer (Jeong et al, *Nature* (1997), 388:860-2; Jeong et al, *J. Control. Release* (2000), 63:155-63; Jeong et al, *Adv. Drug Delivery Rev.* (2002), 54:37-51). The polymer exhibits sol-gel behavior over a concentration of about 5% w/w to about 40% w/w. Depending on the properties desired, the lactide/glycolide molar ratio in the PLGA copolymer ranges from about 1:1 to about 20:1. The resulting copolymers are soluble in water and form a free-flowing liquid at room temperature, but form a hydrogel at body temperature. A commercially available PEG-PLGA-PEG triblock copolymer is RESOMER RGP t50106 manufactured by Boehringer Ingelheim. This material is composed of a PLGA copolymer of 50:50 poly(DL-lactide-co-glycolide) and is 10% w/w of PEG and has a molecular weight of about 6000.

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Additional biodegradable thermoplastic polyesters include AtriGel® (provided by Atrix Laboratories, Inc.) and/or those disclosed, e.g., in U.S. Pat. Nos. 5,324,519; 4,938,763; 5,702,716; 5,744,153; and 5,990,194; wherein the suitable biodegradable thermoplastic polyester is disclosed as a thermoplastic polymer. Examples of suitable biodegradable thermoplastic polyesters include polylactides, polyglycolides, polycaprolactones, copolymers thereof, terpolymers thereof, and any combinations thereof. In some such embodiments, the suitable biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof. In one embodiment, the biodegradable thermoplastic polyester is 50/50 poly(DL-lactide-co-glycolide) having a carboxy terminal group; is present in about 30 wt. % to about 40 wt. % of the composition; and has an average molecular weight of about 23,000 to about 45,000. Alternatively, in another embodiment, the biodegradable thermoplastic polyester is 75/25 poly (DL-lactide-co-glycolide) without a carboxy terminal group; is present in about 40 wt. % to about 50 wt. % of the composition; and has an average molecular weight of about 15,000 to about 24,000. In further or alternative embodiments, the terminal groups of the poly(DL-lactide-co-glycolide) are either hydroxyl, carboxyl, or ester depending upon the method of polymerization. Polycondensation of lactic or glycolic acid provides a polymer with terminal hydroxyl and carboxyl groups. Ring-opening polymerization of the cyclic lactide or glycolide monomers with water, lactic acid, or glycolic acid provides polymers with the same terminal groups. However, ring-opening of the cyclic monomers with a monofunctional alcohol such as methanol, ethanol, or 1-dodecanol provides a polymer with one hydroxyl group and one ester terminal groups. Ring-opening polymerization of the cyclic monomers with a diol such as 1,6-hexanediol or polyethylene glycol provides a polymer with only hydroxyl terminal groups.

Since the polymer systems of thermosetting gels dissolve more completely at reduced temperatures, methods of solubilization include adding the required amount of polymer to the amount of water to be used at reduced temperatures. Generally after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostatic container at about 0-10° C. in order to dissolve the polymer. The mixture is stirred or shaken to bring about a more rapid dissolution of the thermosetting gel polymer. The ophthalmic agent and various additives such as buffers, salts, and preservatives are subsequently added and dissolved. In some instances the pharmaceutically agent is suspended if it is insoluble in water. The pH is modulated by the addition of appropriate buffering agents.

Ophthalmic Ointment Muscarinic Antagonist Composition

An ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (e.g. oil 80%-water 20%) with a high viscosity, intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that it contains. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an eye ointment), vulva, anus, and nose

The vehicle of an ointment is known as the ointment base. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are:

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hydrocarbon bases, e.g. hard paraffin, soft paraffin, micro-crystalline wax and ceresine; absorption bases, e.g. wool fat, beeswax; water soluble bases, e.g. macrogols 200, 300, 400; emulsifying bases, e.g. emulsifying wax, cetrimide; vegetable oils, e.g. olive oil, coconut oil, sesame oil, almond oil and peanut oil.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. In some embodiments, they are also derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases. The active agents are dispersed in the base, and later they get divided after the drug penetration into the target sites (e.g. membranes, skins, etc.).

The present disclosure recognizes that it is sometimes difficult to incorporate into the ointment a drug of low concentration with sufficient dose-to-dose uniformity for effectively treating a disorder or disease. In some embodiments, poly(ethylene-glycols), polyethoxylated castor oils (Cremophor® EL), alcohols having 12 to 20 carbon atoms or a mixture of two or more of said components are effective excipients for dispersing and/or dissolving effective amounts of ophthalmic drugs, in particular of ascomycins and staurosporine derivatives, in an ointment base, in particular in an ointment base substantially comprising oleaginous and hydrocarbon components, and that the resulting ointments are excellently tolerated by the skin and by ocular tissue.

The present disclosure further recognizes that ophthalmic drugs, such as a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), incorporated in the ointment compositions describes herein target the choroid and/or retina in a patient when the compositions are topically administered to the ocular surface, in particular to the sclera of said patient. In some embodiments, an ophthalmic ointment composition includes an ophthalmic drug, an ointment base and an agent for dispersing and/or dissolving said drug in the ointment base, selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components.

In some embodiments, the ointment bases include ophthalmically acceptable oil and fat bases, such as natural wax e.g. white and yellow bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax e.g. hard paraffin, microcrystalline wax; hydrocarbons e.g. liquid paraffin, white and yellow soft paraffin, white petrolatum, yellow petrolatum; or combinations thereof.

The above mentioned oil and fat bases are described in more detail, for instance, in the British Pharmacopoeia, Edition 2001, or the European Pharmacopoeia, 3rd Edition.

In some embodiments, the ointment base is present in amounts of about 50 to about 95, preferably of 70 to 90% by weight based on the total weight of the composition.

A preferred ointment base comprises a combination of one or more of one or more natural waxes like those indicated above, preferably wool wax (wool fat), and one or more hydrocarbons like those indicated above, preferably a soft paraffin or a petrolatum, more preferably in combination with liquid paraffin.

A special embodiment of the aforementioned ointment base comprises e.g. 5 to 17 parts by weight of wool fat, and 50 to 65 parts by weight of white petrolatum as well as 20 to 30 parts by weight of liquid paraffin.

In some embodiments, the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base is selected from a poly(ethylene-glycol), a polyethoxylated

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castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components. The agent is preferably used in amounts of 1 to 20 percent, more preferably 1 to 10 percent by weight of the entire semisolid ophthalmic composition.

Alcohols having 12 to 20 carbon atoms include particularly stearyl alcohol (C₁₈H₃₇OH), cetyl alcohol (C₁₆H₃₃OH) and mixtures thereof. Preferred are so-called cetostearyl alcohols, mixtures of solid alcohols substantially consisting of stearyl and cetyl alcohol and preferably comprising not less than 40 percent by weight of stearyl alcohol and a sum of stearyl alcohol and cetyl alcohol amounting to at least 90 percent by weight, and compositions comprising not less than 80 percent by weight of cetylstearyl alcohol and an emulsifier, in particular sodium cetostearyl sulfate and/or sodium lauryl sulfate, preferably in amounts not less than 7 percent by weight of emulsifier.

Polyethoxylated castor oils are reaction products of natural or hydrogenated castor oils and ethylene glycol. In some instances, such products are obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:30 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable and preferred is a product commercially available under the trade name Cremophor® EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an nD₂₅=ca. 1.471. Also suitable for use in this category is, for instance, Nikkol® HCO-60, a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0° C.; Freezing point=ca. 32.4° C.; H₂O content (% KF)=ca. 0.03.

Poly(ethylene-glycols) are used in some embodiments as the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base according to the present disclosure. Suitable poly(ethylene-glycols) are typically mixtures of polymeric compounds of the general formula H—(OCH₂CH₂)_nOH, wherein the index n typically range from 4 to 230 and the mean molecular weight from about 200 to about 10000. Preferably n is a number from about 6 to about 22 and the mean molecular weight between about 300 and about 1000, more preferably n ranges from about 6 to about 13 and the mean molecular weight from about 300 to about 600, most preferably n has a value of about 8.5 to about 9 and the relative molecular weight is about 400. Suitable poly(ethylene-glycols) are readily available commercially, for example poly(ethylene-glycols) having a mean molecular weight of about 200, 300, 400, 600, 1000, 1500, 2000, 3000, 4000, 6000, 8000 and 10000.

The poly(ethylene-glycols), in particular the preferred types described in the foregoing paragraph, are preferably used in amounts of 1 to 10, more preferably 1 to 5 percent by weight of the entire semisolid ophthalmic composition.

An especially preferred embodiment of the compositions according to the instant disclosure comprises an agent for dispersing and/or dissolving of the drug in the ointment base which is selected from a poly(ethylene-glycol), a polyethoxylated castor oil and preferably a mixture of said components.

Gel/Ointment Viscosity

In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10,000 to about 300,000 cps

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at about 20° C. and shear rate of 1 s. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 15,000 to about 200,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 50,000 to about 150,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 70,000 to about 130,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 90,000 to about 110,000 cps at about 20° C. and shear rate of 1 s⁻¹.

In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 1,000,000 centipoise, between about 750 and 1,000,000 centipoise; between about 1000 and 1,000,000 centipoise; between about 1000 and 400,000 centipoise; between about 2000 and 100,000 centipoise; between about 3000 and 50,000 centipoise; between about 4000 and 25,000 centipoise; between about 5000 and 20,000 centipoise; or between about 6000 and 15,000 centipoise. In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 50,000 and 1,000,000 centipoise.

In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

In some embodiments, the compositions described herein are viscous compositions at body temperature. In some embodiments, viscous compositions contain from about 10% to about 25% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 14% to about 22% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 15% to about 21% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 100,000 cP to about 1,000,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 150,000 cP to about 500,000 cP. In some embodi-

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ments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 250,000 cP to about 500,000 cP. In some of such embodiments, a viscous ophthalmic composition is a liquid at room temperature and gels at about between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42° C.). In some embodiments, a viscous ophthalmic composition is administered as monotherapy for treatment of an ophthalmic disease or condition described herein.

In some embodiments, the viscosity of the gel formulations presented herein is measured by any means described. For example, in some embodiments, an LVDV-II+CP Cone Plate Viscometer and a Cone Spindle CPE-40 is used to calculate the viscosity of the gel formulation described herein. In other embodiments, a Brookfield (spindle and cup) viscometer is used to calculate the viscosity of the gel formulation described herein. In some embodiments, the viscosity ranges referred to herein are measured at room temperature. In other embodiments, the viscosity ranges referred to herein are measured at body temperature (e.g., at the average body temperature of a healthy human).

Gel/Ointment Dose-to-Dose Uniformity

Typical ophthalmic gels are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. Furthermore, typical ophthalmic ointments are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

In some cases, described herein include ophthalmic gel compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some cases, described herein include ophthalmic ointment compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent con-

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centration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

Methods of Treatment

Disclosed herein are methods of arresting myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above. Also disclosed herein are methods of preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above.

In some embodiments, the ophthalmic aqueous formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous formulation includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic gel formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic ointment formulations described herein are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous formulation described herein is one drop of the aqueous composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodi-

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ments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

In some embodiments of the disclosed method, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 2° C., about 3° C., about 4° C., about 5° C., about 6° C., about 7° C., about 8° C., about 9° C., or about 10° C. prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use.

In some embodiments of the disclosed method, the ophthalmic composition is stored at room temperature after first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 16° C. to about 26° C. after to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 16° C., about 17° C., about 18° C., about 19° C., about 20° C., about 21° C., about 22° C., about 23° C., about 24° C., about 25° C., or about 26° C. after to first use.

In some embodiments, the ophthalmic aqueous formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of the aqueous formulation (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic gel formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of gel (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic ointment formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a small amount of ointment (approximately 0.25 inches) was applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years.

In some embodiments, the ophthalmic composition is administered in doses having a dose-to-dose ophthalmic agent concentration variation of less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

The number of times a composition is administered to an individual in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the individual’s response to the formulation. In some embodiments, a composition disclosed herein is administered once to an individual in need thereof with a mild acute condition. In some embodiments, a composition disclosed herein is administered more than once to an individual in need thereof with a moderate or severe acute

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condition. In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of an ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the ophthalmic agent is given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is from 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

Once improvement of the patient's ophthalmic conditions has occurred, a maintenance ophthalmic agent dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is optionally reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The amount of ophthalmic agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, according to the particular circumstances surrounding the case, including, e.g., the specific ophthalmic agent being administered, the route of administration, the condition being treated, the target area being treated, and the subject or host being treated. The desired dose is presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals.

In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

Kits/Articles of Manufacture

The disclosure also provides kits for preventing or arresting myopia development. Such kits generally will comprise one or more of the ophthalmic compositions disclosed herein, and instructions for using the kit. The disclosure also contemplates the use of one or more of the ophthalmic compositions, in the manufacture of medicaments for treating, abating, reducing, or ameliorating the symptoms of a disease, dysfunction, or disorder in a mammal, such as a human that has, is suspected of having, or at risk for developing myopia.

In some embodiments, kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In other embodiments, the containers are formed from a variety of materials such as glass or plastic.

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The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are also presented herein. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, drop bottles, tubes, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of ophthalmic compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that benefits by controlled release administration of an ophthalmic agent to the eye.

In some embodiments, a kit includes one or more additional containers, each with one or more of various materials (such as rinses, wipes, and/or devices) desirable from a commercial and user standpoint for use of a formulation described herein. Such materials also include labels listing contents and/or instructions for use and package inserts with instructions for use. A set of instructions is optionally included. In a further embodiment, a label is on or associated with the container. In yet a further embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In other embodiments a label is used to indicate that the contents are to be used for a specific therapeutic application. In yet another embodiment, a label also indicates directions for use of the contents, such as in the methods described herein.

In certain embodiments, the ophthalmic compositions are presented in a dispenser device which contains one or more unit dosage forms containing a compound provided herein. In a further embodiment, the dispenser device is accompanied by instructions for administration. In yet a further embodiment, the dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In another embodiment, such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In yet another embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

Example 1—Ophthalmic Formulations

Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-8.

TABLE 1

Aqueous Solution Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9

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TABLE 1-continued

Aqueous Solution Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 2

Aqueous Solution Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 3

Aqueous Solution Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.05-0.15	0.005-0.015 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 4

Mucus Penetrating Particle Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	—	q.s. to formulate atropine at 0.001-0.05 wt %
Deuterated Water	—	q.s. to 100 wt %

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TABLE 5

Mucus Penetrating Particle Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	—	q.s. to formulate atropine at 0.001-0.05 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 6

Cellulose Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine Sulfate	0.01-0.5	0.001-0.05 (wt %)
Viscosity enhancing agent (e.g. hydroxypropyl methylcellulose)	10-50	1-5 (wt %)
Buffer agent and/or pD adjusting agent (e.g., sodium acetate and/or DCl)	—	q.s. for pD = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Deuterated Water	—	q.s. to 100 wt %

TABLE 7

Thermosetting Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Viscosity enhancing agent (e.g. poloxamer 407)	100-250	10-25 (wt %)
Buffer agent and/or pD adjusting agent (e.g., sodium acetate and/or DCl)	—	q.s. for pH = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Deuterated Water	—	q.s. to 100 wt %

TABLE 8

Ointment Formulation (Atropine Sulfate)		
Ingredient	Quantity (g) for 1000 mL solution	Concentration in 1000 mL aqueous solution
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Dispersing agent (e.g. polyethyleneglycol, and/or polyethoxylated castor oil and/or C12-C20 alcohol	10-200	1-20 (wt %)

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TABLE 8-continued

Ointment Formulation (Atropine Sulfate)		
Ingredient	Quantity (g) for 1000 mL solution	Concentration in 1000 mL aqueous solution
Buffering agent pD adjusting agent (e.g. DCl)	—	q.s. for pD = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Ointment base (e.g. wool wax and/or petrolatum and/or liquid paraffin)		q.s. to 100 wt %

Example 2—Preparation of an Aqueous Solution
Formulation Containing 0.01% Atropine in D₂O

Stock 1% Solution

In a 100 mL solution, 1 gram of atropine, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) are added along with a quantity sufficient to equal 100 mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron pothysulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

Diluted 0.01% Solution

0.3 mL of the 1% solution was combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 3—Preparation of an Aqueous Solution
Formulation Containing 0.01% Atropine Sulfate

Stock 1% Solution

In a 100 mL solution, 1 gram of atropine sulfate, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) were added along with a quantity sufficient to equal 100 mL sterile water for injection. The solution was mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders had dissolved and the solution became clear with no visible particles. Next, the stir bar was removed, and the solution was poured into a filter bottle and vacuum filtered through a 0.22 micron pothysulfone membrane filter into a sterile bottle. The filter top was removed from the sterile stock bottle and the stock bottle was capped for storage with a sterile bottle cap.

Diluted 0.01% Solution

0.3 mL of the 1% solution was combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

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Example 4—Stability Analysis

Five 0.01% atropine sulfate solutions were prepared from the 1% atropine sulfate stock solution (preparation as described in Example 2). The pH of the five solutions was 5.87, 5.97, 5.90, 6.24, and 6.16 for solutions 1-5, respectively. Each solution was thoroughly mixed. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers according to Table 9.

TABLE 9

Container Filling Outline		
Type of Container	Volume of 0.01% Atropine Sulfate Drug Product in Container	Total Containers Filled
Sterile Eyedroppers	5-mL	12
Sterile Glass Vials	5-mL	12

The samples were then stored at different conditions for stability analysis. The samples were analyzed at different time points up to 2 months. The storage conditions include: 40° C. with 75% relative humidity (RH) (samples were transferred from 2-8° C. condition after 3 days), 25° C. with 60% RH, and 60° C. The time points were 1 week, 2 weeks, 1 month, and 2 months. At each of the time point, one plastic eyedropper (LDPE plastic) and one glass vial from each of the stored condition were removed and allowed to equilibrate to ambient conditions. Once equilibrated, both the plastic eyedropper and the glass vials were inverted 3 times. The solution in the eyedroppers was transferred to an HPLC vial in a drop wise fashion through the dropper. The solution in the glass vial was aliquotted into an HPLC vial using a glass Pasteur pipette. The samples were then tested for purity and potency using the UPLC method listed in Table 10.

TABLE 10

UPLC Method Parameters	
Parameter	Condition
Column	EMD, Hiber HR PurospherSTAR C-18, 100 × 2.1 mm, 2 μm
Mobile Phase/Diluent	87:13, 50 mM Potassium Phosphate: Acetonitrile, pH 3.5
Flow	Isocratic
Flow Rate	0.5 mL/min
Detection Wavelength	210 nm
Column Temperature	30 ± 3° C.
Autosampler Temperature	5 ± 3° C.
Run Time	6.0 minutes
Injection Volume	10 μL*
Needle Wash Solution	90/10 Water:Acetonitrile

*Modified from original method to maintain sensitivity at 100 μg/mL nominal.

Table 11 lists the stability data for the 0.01% atropine sulfate solutions.

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TABLE 11

Stability Data for 0.01% Atropine Sulfate Solutions															
Analyst	Container Type	Storage Condition	t = 0			t = 1 week		t = 2 week ¹		t = 1 month ²			t = 2 month ³		
			Purity	Po- tency	pH	Purity	Po- tency	Purity	Po- tency	Purity	Po- tency	pH	Purity	Po- tency	pH
1	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.5	99.8	5.9	ND	ND	99.1	99.9	ND	ND	ND	95.4	97.4	6.3
		40° C./75% RH				ND	ND	96.2	97.3	95.1	95.6	5.2	ND	ND	ND
		60° C.				80.8	83.3	86.2	88.6	88.3	91.5	4.2	ND	ND	ND
	Glass Vial	25° C./60% RH	99.8	100.4	ND	ND	ND	92.2	93.1	80.7	80.5	7.8	73.0	74.5	7.3
		40° C./75% RH				ND	ND	73.6	74.1	50.1	50.2	7.4	ND	ND	ND
		60° C.				43.1	43.9	28.3	28.4	ND	ND	ND	ND	ND	ND
2	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.7	99.9	6.0	ND	ND	99.1	99.6	ND	ND	ND	97.0	99.1	6.1
		40° C./75% RH				ND	ND	96.6	97.2	95.5	95.8	5.6	ND	ND	ND
		60° C.				89.4	92.2	92.2	94.0	90.6	94.4	4.1	ND	ND	ND
	Glass Vial	25° C./60% RH	99.8	100.2	ND	ND	ND	92.6	92.9	82.5	82.2	7.6	80.2	81.6	7.3
		40° C./75% RH				ND	ND	74.7	75.1	59.1	59.0	7.2	ND	ND	ND
		60° C.				54.2	55.2	37.3	37.4	ND	ND	ND	ND	ND	ND
3	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.3	96.3	5.9	ND	ND	98.7	96.1	ND	ND	ND	95.8	94.8	6.3
		40° C./75% RH				ND	ND	96.7	93.1	94.8	91.8	5.5	ND	ND	ND
		60° C.				88.8	89.0	88.0	86.8	88.6	87.7	4.1	ND	ND	ND
	Glass Vial	25° C./60% RH	99.4	98.4	ND	ND	ND	94.1	91.2	85.0	81.9	7.5	79.3	78.3	7.3
		40° C./75% RH				ND	ND	72.2	74.6	61.3	63.0	7.2	ND	ND	ND
		60° C.				48.6	51.1	34.1	34.9	ND	ND	ND	ND	ND	ND
4	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.8	99.6	6.2	ND	ND	99.1	98.8	ND	ND	ND	96.4	97.6	6.3
		40° C./75% RH				ND	ND	96.3	97.0	94.5	94.2	5.6	ND	ND	ND
		60° C.				90.5	93.0	89.3	90.6	84.2	85.8	4.2	ND	ND	ND
	Glass Vial	25° C./60% RH	99.8	98.8	ND	ND	ND	90.7	90.0	76.9	75.1	7.6	72.5	71.6	7.4
		40° C./75% RH				ND	ND	71.0	68.7	57.0	56.7	7.2	ND	ND	ND
		60° C.				52.4	52.1	29.7	28.6	ND	ND	ND	ND	ND	ND
5	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.6	100.5	6.2	ND	ND	99.3	100.4	ND	ND	ND	97.8	100.5	6.2
		40° C./75% RH				ND	ND	95.9	96.7	96.8	97.6	5.5	ND	ND	ND
		60° C.				91.2	94.6	91.4	93.6	90.3	92.8	4.2	ND	ND	ND
	Glass Vial	25° C./60% RH	99.8	100.7	ND	ND	ND	90.5	91.3	79.3	79.7	7.8	72.8	74.6	7.3
		40° C./75% RH				ND	ND	71.3	71.9	56.0	56.4	7.3	ND	ND	ND
		60° C.				46.3	47.4	29.5	29.6	ND	ND	ND	ND	ND	ND

¹The 25° C. and the 60° C. samples were pulled at 15 days, the 40° C. samples were pulled at 11 days.²The 25° C. and the 60° C. samples were pulled at 28 days, the 40° C. samples were pulled at 24 days.³The 25° C. and the 60° C. samples were pulled at 46 days.

A change in the pH of the 0.01% Atropine Sulfate solutions was observed over the course of the stability study. The plastic (LDPE) eyedroppers maintained pH around 6.2 when stored at 25° C. for 2 months. However at the same time point, the pH of the 0.01% atropine has increased to 7.2 when stored in glass vials. Additionally, when stored at elevated temperatures (e.g. 40° C. and 60° C.), the pH in the plastic (LDPE) eyedroppers dropped to approximately 4-5, while the pH maintained around 7.2 when stored in the glass vials.

There was also a significant difference in the rate of degradation for Atropine Sulfate (0.01%) when stored in plastic (LDPE) eyedroppers versus Type I glass vials. However, in both containers there was an increase of an early eluting related substance at relative retention time (RRT)=0.87-0.89. In some cases, this early eluting related substance is referred to as primary degradant. In some instances, the primary degradant is referred to as RRT 0.87-0.89. This related substance is likely to be the first parameter to fail specification regardless of the container. The amount of this related substance was tracked at each time point and is listed in Table 12.

TABLE 12

Area (%) of the Main Degradation Species for 0.01% Atropine Sulfate (RRT 0.87-0.89)						
Analyst	Temperature ° C.	t = 0	t = 1 week	t = 2 week	t = 1 month	t = 2 months
1	25	0.08	NA	0.92	NA	3.98
	40	NA	NA	3.74	4.78	NA
	60	NA	17.78	13.49	11.51	NA

TABLE 12-continued

Area (%) of the Main Degradation Species for 0.01% Atropine Sulfate (RRT 0.87-0.89)						
Analyst	Temperature ° C.	t = 0	t = 1 week	t = 2 week	t = 1 month	t = 2 months
2	25	0.07	NA	0.88	NA	2.46
	40	NA	NA	3.26	4.37	NA
	60	NA	9.38	7.67	9.13	NA
3	25	0.07	NA	1.05	NA	2.88
	40	NA	NA	2.98	4.85	NA
	60	NA	9.59	11.57	10.55	NA
4	25	0.08	NA	0.92	NA	3.09
	40	NA	NA	3.43	5.32	NA
	60	NA	8.30	10.46	15.49	NA
5	25	0.08	NA	0.64	NA	1.66
	40	NA	NA	3.96	3.07	NA
	60	NA	7.61	8.35	9.7	NA
Average	25° C.	0.08	NA	0.88	NA	2.81
	40° C.	NA	NA	3.47	4.48	NA
	60° C.	NA	10.53	10.31	11.28	NA

Arrhenius based shelf life predictions were calculated using the related substance data from Table 12. These predictions are based on an assumption that the degradation is first order (linear). These predictions are illustrated in FIGS. 1 and 2. FIG. 1 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 40° C. The pH range of the atropine sulfate solution is from 5.9-6.2. FIG. 2

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shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 60° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

Example 5—1% Atropine Sulfate (Bausch+Lomb)
Sample Analysis

The 1% atropine sulfate sample was obtained from Bausch+Lomb (Lot 198421). For comparison the pH of the 1% Atropine Sulfate drug product was determined in the neat solution as well as a sample that was diluted to the current nominal concentration (0.01% Atropine Sulfate) using the vehicle. Additionally a sample was diluted to the nominal concentration with method diluent. Both samples diluted to the nominal concentration were analyzed using the RP-UPLC method (Table 10). The results are listed in Table 13.

TABLE 13

pH and Purity of the Bausch + Lomb Atropine Sulfate Sample		
Sample	pH	Purity (% area)
1% Atropine Sulfate	4.89	ND
0.01% Atropine Sulfate, diluted with Vehicle	6.16	99.6%
0.01% Atropine Sulfate, diluted with Diluent	ND	99.6%
Vehicle	7.94	ND

ND = not determined

Example 6—Dose Uniformity (10-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 10 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 7—Dose Uniformity (5-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 5 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 8—Dose Uniformity (2-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 2 drops of the aqueous composition

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are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 9—Formulation Stability Comparison

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Eight formulations illustrated in Table 14A were analyzed at t=0, 2 weeks, and 4 weeks. A RP-HPLC method was used to carry out the analysis.

TABLE 14A

Atropine sulfate formulations							
Formulation	Atropine Sulfate Mono-hydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	—	4.2	SWFI
2	0.025	0.01	0.90	0.01	—	4.2	SWFI
3	0.010	0.01	0.90	0.01	—	4.8	SWFI
4	0.025	0.01	0.90	0.01	—	4.8	SWFI
5	0.010	0.01	0.90	—	0.04	5.8	SWFI
6	0.025	0.01	0.90	—	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	—	5.2	D ₂ O (pD)
8	0.010	0.01	0.90	—	0.04	6.2	D ₂ O (pD)

The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware. The pD of Formulation 7 and Formulation 8 are 5.2 and 6.2, respectively. In some instances, the pD is calculated as pD=0.4+pH*, in which pH* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

Table 14B illustrates analysis time points for the formulations listed in Table 14A.

TABLE 14B

Schedule for atropine sulfate formulation testing			
Storage	Time Point		
Condition (Horizontal)	Initial (t = 0)	2 Week	4 Week
25° C./60% RH	X	X	X
40° C./75% RH		X	X
60° C.		X	X

Table 15 illustrates the atropine sulfate purity data associated with each of the eight formulations. Purity is indicated as percentage of area under the curve.

TABLE 15

Atropine sulfate purity as Area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks ¹
Formulation 1	25/60	97.39	97.76	98.20
pH 4.2	40/75		97.25	97.04
	60° C.		94.98	93.87
Formulation 2	25/60	98.85	99.03	99.08
pH 4.2	40/75		98.50	98.32
	60° C.		97.47	96.65

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TABLE 15-continued

Atropine sulfate purity as Area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks ¹
Formulation 3 pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60° C.		95.94	94.65
Formulation 4 pH 4.8	25/60	98.81	98.75	98.46
	40/75		98.26	98.01
	60° C.		96.22	94.04
Formulation 5 pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60° C.		80.94	66.83
Formulation 6 pH 5.8	25/60	99.08	98.91	98.46
	40/75		97.65	96.20
	60° C.		89.15	80.68
Formulation 7 pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60° C.		96.70	94.01
Formulation 8 pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60° C.		95.97	92.72

¹Some chromatographic interference were observed to occur late in the run (~27-32 minutes) for many of the t = 4 week stability samples and in some instances is proposed to be system related.

After four weeks of storage at 60° C., in some instances the atropine sulfate concentration have an impact on the stability for the formulations containing acetic acid at pH 4.2. For example, atropine sulfate concentration at 0.025% w/v (Formulation 2) showed a 2.8% increase in % purity at pH 4.2 compared to the atropine sulfate concentration at 0.010% w/v (Formulation 1). This trend was not observed for the acetic acid formulations at pH 4.8 (Formulations 3 and 4); rather a 0.6% decrease in % purity was observed for the higher doses.

The dose dependent stability trend that was observed at pH=4.2 was also seen in the formulations containing citric acid at pH 5.8 (Formulations 5 and 6). After four weeks of storage at 60° C. there is approximately 14% less degradation in the higher does than observed in the lower dose.

At both the high and the low doses, more degradation is observed in the formulations that start at a higher pH. This degradation is predominantly the growth of tropic acid. In some instances, buffer species plays a role in the observed degradation between the different pH values.

The percentage of tropic acid observed for each of the formulations at t=4 weeks and at 60° C. are as follow:

- Formulation 1-Tropic acid observed is 0.54%.
- Formulation 2-Tropic acid observed is 0.93%.
- Formulation 3-Tropic acid observed is 1.58%.
- Formulation 4-Tropic acid observed is 3.03%.
- Formulation 5-Tropic acid observed is 29.13%.
- Formulation 6-Tropic acid observed is 16.84%.
- Formulation 7-Tropic acid observed is 1.07%.
- Formulation 8-Tropic acid observed is 4.03%.

In some embodiments, switching the water source to deuterated water (D₂O) has an impact on stabilizing the growth of the tropic acid peak for the formulation containing acetic acid at pD 5.2 (Formulation 7), see FIG. 4. In addition, in the formulation containing citric acid at pD 6.2 (Formulation 8), the deuterated water also stabilizes atropine sulfate, see FIG. 5.

Table 16 illustrates tropic acid as area under the curve for each of the eight formulations. Tropic acid is a degradant of atropine sulfate. In some instances, LOQ was previously found to be 0.05% for the RP-HPLC method.

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TABLE 16

Tropic acid as area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 pH 4.2	25/60	<LOQ	0.08	<LOQ
	40/75		0.10	0.10
	60° C.		0.37	0.51
Formulation 2 pH 4.2	25/60	<LOQ	0.05	<LOQ
	40/75		0.11	0.12
	60° C.		0.46	0.93
Formulation 3 pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60° C.		0.90	1.58
Formulation 4 pH 4.8	25/60	<LOQ	0.10	0.13
	40/75		0.31	0.53
	60° C.		1.84	3.03
Formulation 5 pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60° C.		16.62	29.13
Formulation 6 pH 5.8	25/60	<LOQ	0.24	0.42
	40/75		1.30	2.44
	60° C.		9.32	16.84
Formulation 7 pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60° C.		0.71	1.07
Formulation 8 pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60° C.		2.32	4.03

Table 17 illustrates percentage of potency of atropine in the eight formulations.

TABLE 17

% Potency				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 pH 4.2	25/60	109.4	110.3	112.8
	40/75		111.0	112.4
	60° C.		112.8	114.8
Formulation 2 pH 4.2	25/60	102.9	107.1	109.7
	40/75		108.4	109.6
	60° C.		109.4	111.0
Formulation 3 pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60° C.		108.0	109.9
Formulation 4 pH 4.8	25/60	102.5	107.9	109.2
	40/75		107.4	108.9
	60° C.		107.9	108.8
Formulation 5 pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60° C.		90.2	77.7
Formulation 6 pH 5.8	25/60	107.2	107.1	109.1
	40/75		106.8	107.1
	60° C.		99.0	93.7
Formulation 7 pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60° C.		111.8	113.5
Formulation 8 pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60° C.		101.6	103.0

After 4 weeks of storage, the observed potency values were elevated from the t=0 and 2 week time points, with the exception of Formulations 5 and 6 at 60° C. where the potencies dropped due to degradation. In some instances, these potency values are within the error of the HPLC method, but appear to be trending upward. Mass balance was calculated for the 60° C. data and results were consistent across the formulations and levels of degradation, although skewed lower due to the higher than anticipated potency values at 4 weeks, see FIG. 3.

Table 18 illustrates pH or pD stability of the eight formulations.

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TABLE 18

pH/pD Stability				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 (pH)	25/60	4.21	3.93	4.02
	40/75		3.86	3.96
	60° C.		3.71	3.86
Formulation 2 (pH)	25/60	4.26	4.11	4.25
	40/75		4.04	4.17
	60° C.		3.93	4.10
Formulation 3 (pH)	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60° C.		4.32	4.40
Formulation 4 (pH)	25/60	4.98	4.93	5.05
	40/75		4.89	4.98
	60° C.		4.77	4.77
Formulation 5 (pH)	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60° C.		5.82	5.78
Formulation 6 (pH)	25/60	5.80	5.69	5.77
	40/75		5.65	5.67
	60° C.		5.54	5.50
Formulation 7 (pD)	25/60	5.31	5.10	5.24
	40/75		5.08	5.15
	60° C.		5.00	4.93
Formulation 8 (pD)	25/60	6.25	5.72	5.88
	40/75		5.74	5.78
	60° C.		5.58	5.50

The italicized values are pD values for a deuterated sample. In some embodiments, the pD of the deuterated samples are $pD = pH_{reading} + 0.4$ (Glasoe, et al. "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

At the two lower temperatures, the pH values at t=4 week are slightly elevated from the t=2 week time point. These data were generated using a new glass pH probe. In some instances, the observed differences are due to the probe differences or additional variables such as for example, the age of the standard buffers or temperature gradients within the laboratory environment. The downward pH trend for each formulation with increasing temperatures at t=4 week is consistent with previous data and is consistent with the increase in the amount of tropic acid present in the stability sample.

Example 10-Determination of Shelf Life and Activation Energy

Activation energy was calculated for the eight formulations disclosed in Example 9 and comparison with a reference standard was made with Formulations 4-7.

Table 19 illustrates the activation energy (Ea) calculation. The Ea minimum is 17.8 Kcal/mol, the Ea maximum is 21.3 Kcal/mol, and the Ea mean is 19.5 Kcal/mol. Mean is $\pm 3 \times \text{stdev}$. FIGS. 6 and 7 illustrate the poor correlation between RS and tropic acid with Formulation 4 and Formulation 7, respectively. FIGS. 8 and 9 illustrate improved correlation between RS and tropic acid with Formulation 5 and Formulation 6, respectively. At a lower pH (e.g. pH 4.8 or lower), there was a poor correlation observed (Formulation 4 and Formulation 7). This was due to a slowed hydrolysis and increased alternative degradation pathways. At a higher pH (e.g., pH 5.8 or higher), an improved or better correlation was observed (Formulation 5 and Formulation 6). This was due to the hydrolysis of atropine as the primary degradant. It is noted that the activation energy is for the specific acid catalyzed degradation to tropic acid—the predominant degradation product and degradation mechanism operating at pH 5.8 or higher.

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TABLE 19

Activation energy for total related substance (RS) and tropic acid.			
	Total RS	Tropic Acid	
1	Poor	Poor	
	Corr	Corr	
2	12.2	Poor	
		Corr	
3	Poor	18.3	
	Corr		
4	16.8	18.1	
5	19.8	19.7	
6	19.2	20.0	
7	13.2	15.5	
8	Poor	18.9	
	Corr		
Mean	16.2	18.4	Kcal/mole
Stdev	3.4	1.6	
RSD	21%	9%	

Table 20 illustrates the rate of RS or tropic acid formation per week at 40° C.

TABLE 20

Formulation		Rate 40° C. (total RS %/wk)	Rate 40° C. (Tropic acid %/wk)
Formulation 5	0.01% Atr Citrate pH 5.8	1.16	1.09
Formulation 6	0.025% Atr Citrate pH 5.8	0.72	0.61
Formulation 8	0.01% Atr Citrate pD 6.2 D ₂ O		0.163

Table 21 illustrates the activation energy and predicted shelf life at 30° C. calculated based on Table 20. It is assumed for the calculation that tropic acid and total RS is 5% (self-life).

TABLE 21A

Rate @30° C. (Total RS %/wk)				Estimated Shelf life @30° C. (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.45	0.41	0.38	2.78	3.04	3.33
6	0.28	0.26	0.23	4.47	4.90	5.37
8	—	—	—	—	—	—

TABLE 21B

Rate @30° C. (Tropic acid %/wk)				Estimated Shelf life @30° C. (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.42	0.39	0.35	2.95	3.24	3.54
6	0.24	0.22	0.20	5.28	5.78	6.33
8	0.06	0.06	0.05	19.75	21.64	23.70

At pD 6.2, the deuterated formulation (Formulation 8) has a predicted shelf life of close to 2 years at 30° C.

Table 22 illustrate the predicted shelf life at temperatures of 40° C., 30° C., 25° C., and 2-8° C. for Formulations 4-8 for total RS and tropic acid, respectively.

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TABLE 22

Stability Prediction				Temper-		
Temperature		RS		ature	Tropic Acid	
Formulation	(° C.)	weeks	months	(° C.)	weeks	months
4	40	16.5	4.1	40	7.7	1.9
	30	40.2	10.1	30	20.0	5.0
	25	64.2	16.0	25	33.0	8.3
	2-8	493.4	123.4	2-8	296.8	74.2
5	40	2.8	0.7	40	0.9	0.2
	30	7.9	2.0	30	2.7	0.7
	25	13.7	3.4	25	4.6	1.2
	2-8	151.1	37.8	2-8	50.5	12.6
6	40	5.8	1.4	40	1.7	0.4
	30	15.9	4.0	30	4.8	1.2
	25	27.3	6.8	25	8.4	2.1
	2-8	281.6	70.4	2-8	95.9	24.0
7	40	11.5	2.9	40	16.9	4.2
	30	23.2	5.8	30	38.4	9.6
	25	33.4	8.4	25	59.1	14.8
	2-8	165.7	41.4	2-8	388.2	97.1
8	40	—	—	40	6.2	1.6
	30	—	—	30	17.0	4.3
	25	—	—	25	28.9	7.2
	2-8	—	—	2-8	287.1	71.8

Example 11-Additional Formulation Stability Comparison

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Thirteen formulations illustrated in Table 23A were analyzed. Formulations 1-8 had been analyzed at t=0, 2 weeks, 4 weeks, and 8 weeks. Formulations 9-13 had been analyzed at t=0, 2 weeks, and 4 weeks. The pH values reported herein are the measured pH values obtained using the Thermo Scientific, Orion Dual Star pH/ISE benchtop pH meter and the Orion Double Junction Micro pH probe S/N S01-18520 calibrated with H₂O based standards.

TABLE 23A

Atropine sulfate Formulations							
Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	—	4.2	SWFI
2	0.025	0.01	0.90	0.01	—	4.2	SWFI
3	0.010	0.01	0.90	0.01	—	4.8	SWFI
4	0.025	0.01	0.90	0.01	—	4.8	SWFI
5	0.010	0.01	0.90	—	0.04	5.8	SWFI
6	0.025	0.01	0.90	—	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	—	5.2	D ₂ O (pD)
8	0.010	0.01	0.90	—	0.04	6.2	D ₂ O (pD)
9	0.010	—	0.90	—	0.04	6.8	D ₂ O (pD)
10	0.010	—	0.90	—	0.04	6.4	H ₂ O (control)
11	0.010	—	0.90	—	0.08	6.4	H ₂ O (control)
12	0.010	—	0.90	—	0.04	7.2	D ₂ O (pD)
13	0.010	—	0.90	—	0.04	6.8	H ₂ O (control)

The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware and filled into LDPE

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eye droppers. In some instances, the pD is calculated as pD=0.4+pH*, in which pH* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

Table 23B illustrates analysis time points for the formulations listed in Table 23A.

TABLE 23B

Schedule for atropine sulfate formulation testing			
Storage	Time Point		
Condition (Horizontal)	Initial (t = 0)	2 Week	4 Week
25° C./60% RH	X	X	X
40° C./75% RH		X	X
60° C.		X	X

Table 24A and Table 24B illustrate atropine sulfate purity data associated with the atropine sulfate formulations. Purity is indicated as percentage of area under the curve. The **↑** & **↓** indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 24A

Atropine Sulfate Purity as Area-% for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	98.16	98.16	98.45
↓A H ₂ O pH 4.8	40/75		97.98	97.35
	60° C.		95.94	94.65
Formulation 5	25/60	98.16	97.92	97.54
↓C H ₂ O pH 5.8	40/75		95.88	93.51
	60° C.		80.94	66.83
Formulation 10	25/60	98.66	96.67	95.81
↓C H ₂ O pH 6.4	40/75		91.07	85.27
	60° C.		59.77	42.87
Formulation 11	25/60	99.47	97.87	96.69
↓C(2x) H ₂ O pH 6.4	40/75		90.97	84.26
	60° C.		54.96	34.40
Formulation 13	25/60	97.21	95.42	93.24
↓C H ₂ O pH 6.8	40/75		83.05	73.00
	60° C.		43.99	27.50

TABLE 24B

Atropine Sulfate Purity as Area-% for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	98.93	99.07	98.39
↓A D ₂ O pD 5.2	40/75		98.51	97.55
	60° C.		96.70	94.01
Formulation 8	25/60	98.93	98.95	98.51
↓C D ₂ O pD 6.2	40/75		98.53	97.44
	60° C.		95.97	92.72
Formulation 9	25/60	99.29	98.42	98.07
↓C D ₂ O pD 6.8	40/75		95.20	93.22
	60° C.		75.17	65.97
Formulation 12	25/60	98.53	97.17	95.99
↓C D ₂ O pD 7.2	40/75		90.75	84.64
	60° C.		56.78	46.05

Table 25A and Table 25B illustrate tropic acid formation associated with the atropine sulfate formulations. Tropic acid is a degradant of atropine sulfate, and is indicated as percentage of area under the curve. LOQ was found to be 0.05% for the RP-HPLC method. The **↑** & **↓** indicate the high or low concentration of atropine sulfate monohydrate

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(0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid, respectively.

TABLE 25A

Tropic Acid as Area-% for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	<LOQ	0.12	0.05
↓A H ₂ O pH 4.8	40/75		0.19	0.27
	60° C.		0.90	1.58
Formulation 5	25/60	<LOQ	0.40	0.71
↓C H ₂ O pH 5.8	40/75		2.22	4.35
	60° C.		16.62	29.13
Formulation 10	25/60	0.74	1.90	3.21
↓C H ₂ O pH 6.4	40/75		7.61	13.49
	60° C.		37.44	54.06
Formulation 11	25/60	0.09	1.31	2.64
↓C(2x) H ₂ O pH 6.4	40/75		7.61	14.68
	60° C.		42.43	62.23
Formulation 13	25/60	2.21	3.66	6.11
↓C H ₂ O pH 6.8	40/75		15.47	25.80
	60° C.		53.24	69.34

TABLE 25B

Tropic Acid as Area-% for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	<LOQ	0.07	0.08
↓A D ₂ O pD 5.2	40/75		0.14	0.24
	60° C.		0.71	1.07
Formulation 8	25/60	<LOQ	0.11	0.14
↓C D ₂ O pD 6.2	40/75		0.33	0.65
	60° C.		2.32	4.03
Formulation 9	25/60	0.06	0.55	1.06
↓C D ₂ O pD 6.8	40/75		3.16	6.29
	60° C.		21.09	29.25
Formulation 12	25/60	0.42	1.35	2.62
↓C D ₂ O pD 7.2	40/75		7.27	13.53
	60° C.		38.58	48.15

Table 26A and Table 26B illustrate the percentage of potency of atropine in the formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 26A

Percentage of potency for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	106.3	108.0	109.6
↓A H ₂ O pH 4.8	40/75		108.1	110.0
	60° C.		108.0	109.9
Formulation 5	25/60	105.0	105.9	107.1
↓C H ₂ O pH 5.8	40/75		103.8	103.5
	60° C.		90.2	77.7
Formulation 10	25/60	101.7	100.0	98.0
↓C H ₂ O pH 6.4	40/75		89.4	87.0
	60° C.		63.7	45.7
Formulation 11	25/60	97.5	96.1	94.3
↓C(2x) H ₂ O pH 6.4	40/75		89.4	82.0
	60° C.		55.7	35.20
Formulation 13	25/60	99.4	96.9	94.1
↓C H ₂ O pH 6.8	40/75		85.0	74.0
	60° C.		46.4	29.8

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TABLE 26B

Percentage of potency for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	107.3	111.3	112.9
↓A D ₂ O pD 5.2	40/75		111.6	113.5
	60° C.		111.8	113.5
Formulation 8	25/60	99.0	103.0	105.0
↓C D ₂ O pD 6.2	40/75		104.9	104.7
	60° C.		101.6	103.0
Formulation 9	25/60	101.4	99.9	100.1
↓C D ₂ O pD 6.8	40/75		97.4	93.2
	60° C.		78.7	68.9
Formulation 12	25/60	104.9	103.5	101.6
↓C D ₂ O pD 7.2	40/75		96.9	89.1
	60° C.		62.5	50.9

Table 27A and Table 27B illustrate the stability of pH or pD for the atropine sulfate formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 27A

Stability of pH for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	4.85	4.44	4.61
↓A H ₂ O pH 4.8	40/75		4.41	4.54
	60° C.		4.32	4.40
Formulation 5	25/60	5.87	5.93	6.03
↓C H ₂ O pH 5.8	40/75		5.96	5.96
	60° C.		5.82	5.78
Formulation 10	25/60	6.43	6.41	6.46
↓C H ₂ O pH 6.4	40/75		6.62	6.67
	60° C.		6.01	5.92
Formulation 11	25/60	6.44	6.47	6.72
↓C(2x) H ₂ O pH 6.4	40/75		6.66	6.61
	60° C.		6.27	6.23
Formulation 13	25/60	6.77	6.91	6.91
↓C H ₂ O pH 6.8	40/75		6.65	6.62
	60° C.		6.30	6.19

TABLE 27B

Stability of pD for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	5.31	5.10	5.24
↓A D ₂ O pD 5.2	40/75		5.08	5.15
	60° C.		5.00	4.93
Formulation 8	25/60	6.25	5.72	5.88
↓C D ₂ O pD 6.2	40/75		5.74	5.78
	60° C.		5.58	5.50
Formulation 9	25/60	6.76	6.80	6.81
↓C D ₂ O pD 6.8	40/75		6.78	6.86
	60° C.		6.45	6.24
Formulation 12	25/60	7.25	7.18	7.26
↓C D ₂ O pD 7.2	40/75		7.14	7.15
	60° C.		6.52	6.36

Example 12. Determination of Shelf Life and Activation Energy for Atropine Sulfate Formulations of Example 11

Activation energy was calculated for the atropine sulfate formulations disclosed in Example 11. Specifically, activation energies were calculated from the total % of related substances (RS) at 40° C. and 60° C. (2 point calculations)

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and from tropic acid formation at 40° C. and 60° C. (2 point calculations). These values were then averaged. Table 28 illustrates the activation energy calculation. Table 29 illustrates estimated shelf-lives from the 40° C. rate of formation of % RS and tropic acid, respectively. FIG. 10 illustrates estimated shelf lives for D₂O and H₂O formulations.

TABLE 28

Activation Energy		
Atropine Formulations	Total RS	Tropic Acid
7	14	19
3	16	17
8	20	21
5	14	Poor Corr
6	15	16
Mean	16.3	18.7
Stdev	2.68	1.90
RSD	16%	10%
Poor Corr:	One or more curve had R ² < 0.95	

TABLE 29

Estimated Shelf Life				
Formulation	Estimated Shelf life/mo			
	Total related substances % (limit = 8%)		Tropic acid % (limit = 5%)	
	8° C.	25° C.	8° C.	25° C.
0.01% w/v Atr 0.01% w/v Acetate 0.9% w/v NaCl 0.01% w/v BAK pD 5.2 D ₂ O (Formulation 7)	189	26	1427	147
0.01% w/v Atr 0.01% w/v Acetate 0.9% w/v NaCl 0.01% w/v BAK pH 4.8 H ₂ O (Formulation 3)	211	29	1095	113
0.01% w/v Atr 0.04% w/v Citrate 0.9% w/v NaCl 0.01% w/v BAK pD 6.2 D ₂ O (Formulation 8)	158	22	369.8	38
0.01% w/v Atr 0.04% w/v Citrate 0.9% w/v NaCl 0.01% w/v BAK pH 5.8 H ₂ O (Formulation 5)	37	5.2	54	5.5
0.01% Atr 0.9% w/v NaCl pH 5.9 H ₂ O extemporaneous preparation	13.6	2.6		

Tables 30 illustrate the predicted shelf life at temperatures of 40° C., 30° C., 25° C., and 2-8° C. for Formulations 2-8 for total RS and tropic acid, respectively.

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TABLE 30

Stability Prediction		Temperature					
Formulation	Temperature (° C.)	RS		Tropic Acid	Tropic Acid		
		weeks	months		weeks	months	
2	40	64.5	16.1	40	—	—	
	30	153.2	38.3	30	—	—	
	25	241.2	60.3	25	—	—	
	2-8	1747.9	437.0	2-8	—	—	
3	40	31.1	7.8	40	99.5	24.9	
	30	73.9	18.5	30	268.3	67.1	
	25	116.3	29.1	25	451.8	113.0	
	2-8	842.9	210.7	2-8	4382.0	1095.5	
4	40	30.7	7.7	40	42.1	10.5	
	30	73.0	18.2	30	113.7	28.4	
	25	114.9	28.7	25	191.5	47.9	
	2-8	832.6	208.1	2-8	1857.0	464.2	
5	40	5.5	1.4	40	4.9	1.2	
	30	13.1	3.3	30	13.2	3.3	
	25	20.6	5.2	25	22.2	5.5	
	2-8	149.3	37.3	2-8	215.0	53.8	
6	40	10.7	2.7	40	8.8	2.2	
	30	25.5	6.4	30	23.7	5.9	
	25	40.1	10.0	25	39.8	10.0	
	2-8	290.5	72.6	2-8	386.5	96.6	
7	40	27.9	7.0	40	129.6	32.4	
	30	66.4	16.6	30	349.6	87.4	
	25	104.5	26.1	25	588.7	147.2	
	2-8	757.3	189.3	2-8	5709.4	1427.4	
8	40	23.3	5.8	40	33.6	8.4	
	30	55.3	13.8	30	90.6	22.6	
	25	87.2	21.8	25	152.5	38.1	
	2-8	631.6	157.9	2-8	1479.2	369.8	

Example 13—Forced Degradation Study of Atropine Formulation 8 in D₂O and H₂O Conditions

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) was used for this experiment. A correction factor of 83.3% is used to quantitate amount of free Atropine. Table 31 shows the D₂O and H₂O formulation compositions.

TABLE 31

Formulation 8 Compositions		
Formulation	[Free Atropine] (µg/mL)	Composition
8-D ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in D ₂ O, pD 6.2
8-H ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in H ₂ O, pH 5.8

D₂O-based Formulation 8 and H₂O-based Formulation 8 were subjected to acid, base, light, heat and oxidative stress. Approximately 5-20% degradation was targeted for all stress conditions to produce sufficient degradation while avoiding secondary degradation. At each condition, Formulation 8

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samples were incubated alongside a vehicle control containing BAK. For the light condition, a foil wrapped Formulation 8 control and foil wrapped vehicle control were prepared to understand if extraneous degradation, such as heat in the light box, were to occur. A RP-HPLC method was used to carry out the analysis. Mass balance (the correlation of potency and purity by area-%) was also evaluated using Equation I.

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$$\text{Mass Balance} = \frac{(\text{Potency}_{\text{initial}} + (100 - \text{Purity}_{\text{initial}}))}{(\text{Potency}_{\text{final}} + (100 - \text{Purity}_{\text{final}}))}$$

The forced degradation results were processed at 210 nm, and are presented in Tables 32A and 32B for H₂O and D₂O formulations, respectively.

TABLE 32A

Forced Degradation Results for Formulation 8 - H ₂ O								
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance	
Control	2-8° C., foil wrapped	3 day	100.9	100.0	0.412	0.657	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	23 day	-7.9	-5.9	0.301	0.513	Y	101.8%
Base (0.001N NaOH)	Ambient, foil wrapped	4 hr	-5.2	-6.6	0.417	0.725	Y	98.7%
		6 hr	-7.3	-7.9	0.462	0.741	Y	99.5%
Heat	60° C., foil wrapped	7 day	-12.1	-11.9	0.428	0.478	Y	100.3%
		10 day	-18.4	-18.4	0.476	0.752	Y	100.0%
Light	Ambient, clear glass vial	1.1 million lux hours (10 day)	-10.1	-7.6	0.478	0.831	Y	102.5%
		1.5 million lux hours (14 day)	-19.1	-12.2	0.597	0.911	Y	107.1%
Light Control	Ambient, foil wrapped	1.1 million lux hours (10 day)	-0.4	-0.5	0.411	0.665	Y	99.9%
		1.5 million lux hours (14 day)	-3.0	-0.3	0.388	0.592	Y	102.8%
Oxidation (3% H ₂ O ₂)	Ambient, foil wrapped	3 day	-16.0	-7.9	0.532	0.791	Y	108.8%
		4 day	-28.0	-13.9	0.473	0.777	Y	115.7%
		7 day	-29.4	-13.5	0.705	0.967	Y	118.9%

TABLE 32B

Forced Degradation Results for Formulation 8 - D ₂ O								
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance	
Control	2-8° C., foil wrapped	4 day	106.7	98.3	0.361	0.659	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	17 day	-6.9	-5.5	0.250	0.469	Y	97.9%
Base (0.001N NaOH)	Ambient, foil wrapped	5 day	-2.3	-2.2	0.495	0.849	Y	100.0%
Base (0.005N NaOH)	Ambient, foil wrapped	30 min	-9.7	-9.6	0.601	0.894	Y	100.2%
Heat	60° C., foil wrapped	17 day	-18.1	-16.9	0.281	0.550	Y	101.1%
Light	Ambient, clear glass vial	0.44 million lux hours (4 day)	-14.1	-4.5	0.463	0.733	Y	109.6%

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TABLE 32B-continued

Forced Degradation Results for Formulation 8 - D ₂ O							
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Light Control (foil covered)	0.87 million lux hours (8 day)	-24.2	-11.3	0.528	0.846	Y	113.8%
	0.44 million lux hours (4 day)	-0.2	1.7	0.354	0.640	Y	101.8%
	0.87 million lux hours (8 day)	0.0	1.4	0.330	0.599	Y	101.3%
Oxidation (3% H ₂ O ₂)	Ambient, 4 day	-10.6	-3.0	0.439	0.720	Y	107.5%
	foil wrapped 8 day	-17.9	-8.3	0.385	0.672	Y	109.9%

Example 14—Formulation 8 Stability Comparison

The long-term stability of atropine sulfate formulation 8 in D₂O (see Table 31 for formulation composition) was analyzed at three different storage conditions. Table 33 illustrates the stability criteria: appearance, potency, tropic acid level, total purity, and pD at storage conditions of 25° C. with 60% humidity, 40° C. with 75% humidity, and 60° C. As discussed above, pD=pH_{reading}+0.4 (Glasoe, et al. "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

A comparison of Formula 8 in H₂O and D₂O under three storage conditions is further illustrated in FIG. 11. FIG. 11A shows the presence of tropic acid degradant at 25° C. with 60% humidity. By week 8, about 1.45% of tropic acid was observed in the H₂O formulation while only 0.23% of tropic acid was observed in the D₂O formulation. Similarly, at 40° C. with 75% humidity storage condition (FIG. 11B), 8.34% of tropic acid was observed in the H₂O formulation while only 1.24% of tropic acid was observed in the D₂O formulation by week 8. At 60° C. storage condition (FIG. 11C), 42.8% of tropic acid was observed in the H₂O formulation while only 6.01% of tropic acid was observed in the D₂O formulation by week 8.

TABLE 33

Formulation 8 Stability							
Parameter	Initial	2 weeks	4 weeks	8 weeks	6 months	9 months ²	12 months ³
Storage Condition: 25° C./60% RH							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)	99.2%	103.0%	105.0%	96.0%	99.7%	97.7%	101.7%
Tropic Acid Level	0.05%	0.11%	0.14%	0.23%	0.55%	0.91%	1.24%
Total Purity ¹	98.9%	98.9%	98.5%	98.1%	99.2%	98.4%	97.8%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.9 (pH 5.5)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.7 (pH 5.3)	5.8 (pH 5.4)
Storage Condition: 40° C./75% RH							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)	99.2%	104.8%	104.7%	94.9%	96.6%	94.2%	95.6%
Tropic Acid Level	0.05%	0.34%	0.65%	1.24%	3.32%	5.05%	6.71%
Total Purity ¹	98.9%	98.5%	97.5%	96.6%	96.3%	92.5%	90.5%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.6 (pH 5.2)	5.7 (pH 5.3)	5.5 (pH 5.1)	5.7 (pH 5.3)
Storage Condition: 60° C.							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay) ⁴	99.2%	101.6%	103.0%	92.9%	100.6%	104.0%	115.9%
Tropic Acid Level	0.05%	2.33%	4.02%	6.01%	10.33%	10.87%	12.97%
Total Purity ¹	98.9%	96.0%	92.8%	88.8%	85.5%	78.0%	72.4%
pD	6.3 (pH 5.9)	5.6 (pH 5.2)	5.5 (pH 5.1)	5.2 (pH 4.8)	5.1 (pH 4.7)	4.9 (pH 4.5)	5.0 (pH 4.6)

¹Slight variability is observed in the total purity results due to sensitivity differences from one HPLC system to the next.

²Results reported are from a second aliquot taken from the original assay eyedropper.

³Results reported are from an aliquot taken from the original assay eyedropper.

⁴A growing unknown related substance peak is observed to co-elute with the main peak and is included in the Atropine Sulfate potency result due to a lack of a clear inflection point between the two species upon integration.

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Example 15—Effect of pH on Ophthalmic
Acceptance in Guinea Pigs

A cohort of guinea pigs is administered 50 μ L of ophthalmic formulations having different pH values described herein. For example, ophthalmic formulations comprising H₂O or deuterated water (e.g., D₂O) are administered to the animals. Animal behavior is recorded at predetermined time intervals to evaluate the acceptance of the ophthalmic formulations.

Example 16—In Vivo Rabbit Eye Irritation Test

The exemplary compositions disclosed herein are subjected to rabbit eye irritation test to evaluate their safety profile. The test composition are tested for eye irritation test in New Zealand Rabbits (see for example Abraham M H, et al., Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis. *Toxicol Sci.* 2003 December; 76(2):384-91. Epub 2003 Sep. 26; see also Gettings S D et al., A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations. *Food Chem Toxicol.* 1998 March; 36(3):209-31). The study involves single ocular administration into the right eye and the same volume of its placebo in the left eye of each of the three rabbits. Rabbits are examined immediately and after instillation of the compositions for 4, 24, 48 and 72 hours post instillation to note the signs/symptoms of eye irritation, if any. The test compositions show no sign of irritancy in cornea, iris and conjunctivae of the rabbit eyes.

Example 17—In Vivo Testing of Ophthalmic
Aqueous Formulation in Guinea Pigs

Focus deprivation myopia (FDM) is achieved using a latex shield to cover one eye. For defocus-induced myopia, a latex-made facemask was held in place by a rubber-band around the head of animals, leaving both eyes, the nose, mouth and ears freely exposed. A -4.00 D lens is glued onto a plastic lens frame. The lens frame is then attached to the facemask around one eye by a fabric hook-and-loop fastener after the optical center of the lens was aligned with the pupil center. The lens is detached and cleaned on both sides with a water-wetted gauze at least once daily followed by re-attachment to the facemask. All the animals are maintained on a cycle of 12-h illumination (500 Lux) and 12-h darkness during the experimental period.

A cohort of guinea pigs at age of 3 weeks are randomly assigned to FDM (a facemask worn monocularly) or defocus-induced myopia (a -4.00 D lens worn monocularly) and control groups. The FDM groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or FDM-only. The defocus-induced myopia groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or defocus-only. The control groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or no treatment. Ocular biometric parameters are measured in both eyes of individual animals before and at 11 days of treatment.

Biometric parameters (e.g. refraction, corneal curvature, and axial components of the eye) are measured by an optometrist, orthoptist, or ophthalmologist with help from an animal care assistant during the light cycle (daytime) after

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removal of the facemask or lens. The optometrist, orthoptist, or ophthalmologist is masked in regard to the treatment conditions for each animal.

Refraction is measured by retinoscopy after the pupil is completely dilated by topical administration of 1% cyclopentolate hydrochloride. The results of retinoscopy are recorded as the mean value of the horizontal and vertical meridians.

Corneal curvature is measured with a keratometer modified by attachment of an +8 D lens onto the anterior surface of the keratometer. A group of stainless steel balls with diameters from 5.5 to 11.0 mm are measured by the modified keratometer. Three readings are recorded for each measurement to provide a mean result. The radius of corneal curvature is then deduced from the readings on the balls with known radii.

A-scan ultrasonograph is used to measure axial components of the eye (lens thickness and vitreous length and axial length). The conducting velocity was 1,723.3 m/s for measurement of the lens thickness and 1,540 m/s for measurement of the vitreous length as described previously. Each of the axial components is calculated as the mean of 10 repeated measurements.

Example 18—Safety and Efficacy Studies of
Ophthalmic Aqueous Formulation

A clinical trial is performed to investigate the efficacy and safety of ophthalmic aqueous formulations described herein in patients with myopia. In some instances, the study is open-label, single blind, or double blind study. Patient selection criteria include myopic refraction of at least 1.0D in both eyes, and additional factors such as astigmatism, a documented myopic progression, age, sex, and/or health conditions.

The patients are randomized to receive 0.05%, 0.01%, or 0.001 atropine aqueous formulation formulated in either H₂O or deuterated water (e.g., D₂O) once nightly in both eyes. Allocation ratio in some instances is defined based the patient population.

The patients are evaluated on day 0 (baseline), day 14, day 30, and then at 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, and 36 months. At each visit, best-corrected distance log Mar visual acuity (BCVA) is assessed by an optometrist, orthoptist, or ophthalmologist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity is assessed using best-corrected distance spectacle correction with a reduced log Mar reading chart placed at 40 cm under well-lit conditions. The near point of accommodation (NPA) is measured using a RAF rule using best-corrected distance spectacle correction. Patients are instructed to move the target inwards till the N5 print becomes slightly blurred and then outwards till it just becomes clear. Accommodation amplitude is calculated as the inverse of NPA. Mesopic pupil size is measured with Procyon 3000 pupillometer. Photopic pupil size is measured using the Neuroptics pupillometer.

Cycloplegic autorefraction is determined 30 minutes after 3 drops of cyclopentolate 1% are administered at 5 minutes apart using a Canon RK-F1 autorefractor. A Zeiss IOL Master, a non-contact partial coherence interferometry, is used to measure the ocular axial length.

The primary outcome is myopia progression over the time period of the study. Safety is assessed by adverse events including allergic reactions, irritation, or development of blurring of vision in one or both eyes.

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Example 19—Preparation of an Ointment
Formulation Containing Atropine Sulfate

Atropine sulfate is mixed with the dispersing agent (e.g. polyethyleneglycol) under heating and sonication and this mixture is further thoroughly mixed with a molten ointment base (e.g. a mixture of wool wax, white petrolatum, and liquid paraffin). The mixture is placed in a pressure vessel, and sterilized at 125° C. for 30-45 minutes and cooled to room temperature. In another embodiment, autoclaving is conducted under nitrogen. The resulting ophthalmic ointment is aseptically filled into pre-sterilized containers (e.g. tubes).

Example 20—Atropine-Mucus Penetrating Particle
Composition

A 0.01% atropine-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200 nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15° C. and about 25° C.

Example 21—Atropine Sulfate-Mucus Penetrating
Particle Composition

A 0.01% atropine sulfate-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200 nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also be added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15° C. and about 25° C.

According to another aspect of the disclosure, described herein is an ophthalmic composition that comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate.

In some instances, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

In some instances, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

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In some instances, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

In some instances, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some instances, the storage condition has a storage temperature of one of: about 25° C., about 40° C., or about 60° C. In some cases, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some cases, the storage condition has a relative humidity of about 60% or about 75%.

In some instances, the ophthalmic composition is in the form of an aqueous solution. In some cases, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some instances, the ophthalmic composition further comprises an osmolarity adjusting agent. In some cases, the osmolarity adjusting agent is sodium chloride.

In some instances, the ophthalmic composition further comprises a preservative. In some cases, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some instances, the ophthalmic composition further comprises a buffer agent. In some cases, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some instances, the ophthalmic composition further comprises a tonicity adjusting agent. In some cases, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

In some instances, the ophthalmic composition is stored in a plastic container. In some cases, the material of the plastic container comprises low-density polyethylene (LDPE).

In some instances, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some cases, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some instances, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to

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about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

In some instances, the ophthalmic composition further comprises a pH adjusting agent. In some cases, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

In some instances, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% D₂O. In some cases, the ophthalmic composition is essentially free of D₂O.

In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

In some instances, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some cases, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

In some instances, the ophthalmic composition is not formulated as an injectable formulation.

While preferred embodiments of the present disclosure have been shown and described herein, such embodiments are provided by way of example only. Various alternatives to the embodiments described herein are optionally employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein the stabilized ophthalmic composition is a liquid, and wherein the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.

2. The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.001 wt % to about 0.03 wt %.

3. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition has a pH of about 6.1.

4. The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.01 wt % to about 0.02 wt %.

5. The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of about 0.01 wt %.

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6. The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises a borate, a borate-polyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof.

7. The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof.

8. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a tonicity adjusting agent.

9. The stabilized ophthalmic composition of claim 8, wherein the tonicity adjusting agent comprises a halide salt of a monovalent cation.

10. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises an ophthalmically acceptable viscosity agent.

11. The stabilized ophthalmic composition of claim 10, wherein the ophthalmically acceptable viscosity agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, or hydroxypropylmethyl-cellulose (HPMC).

12. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a preservative.

13. The stabilized ophthalmic composition of claim 12, wherein a concentration of the preservative is from about 0.0001% to about 1%.

14. The stabilized ophthalmic composition of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

15. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

16. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is topically administered.

17. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered by instillation.

18. The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered through an eye drop bottle containing the stabilized ophthalmic composition.

19. A method of treating the pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount of the stabilized ophthalmic composition of claim 1.

* * * * *

(12) **United States Patent**
Ostrow et al.

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- (54) **OPHTHALMIC COMPOSITION**
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- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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CPC **A61K 31/46** (2013.01); **A61K 9/0048** (2013.01); **A61K 47/02** (2013.01)
- (58) **Field of Classification Search**
USPC 514/304
See application file for complete search history.

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(57) **ABSTRACT**

Provided herein is an ophthalmic composition. In some embodiments, the ophthalmic composition includes a low concentration of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. Further disclosed herein include an ophthalmic composition including a low concentration of an ophthalmic agent and deuterated water. Also disclosed herein are methods of arresting or preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described herein.

23 Claims, 13 Drawing Sheets

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Fig. 1A

		Weeks					
	Temp (°C)	0	1	1.571429	2.142857	3.428571	6.571429
T1	25	0.08			0.88		2.81
T2	40	0.08		3.47		4.48	

Fig. 1B

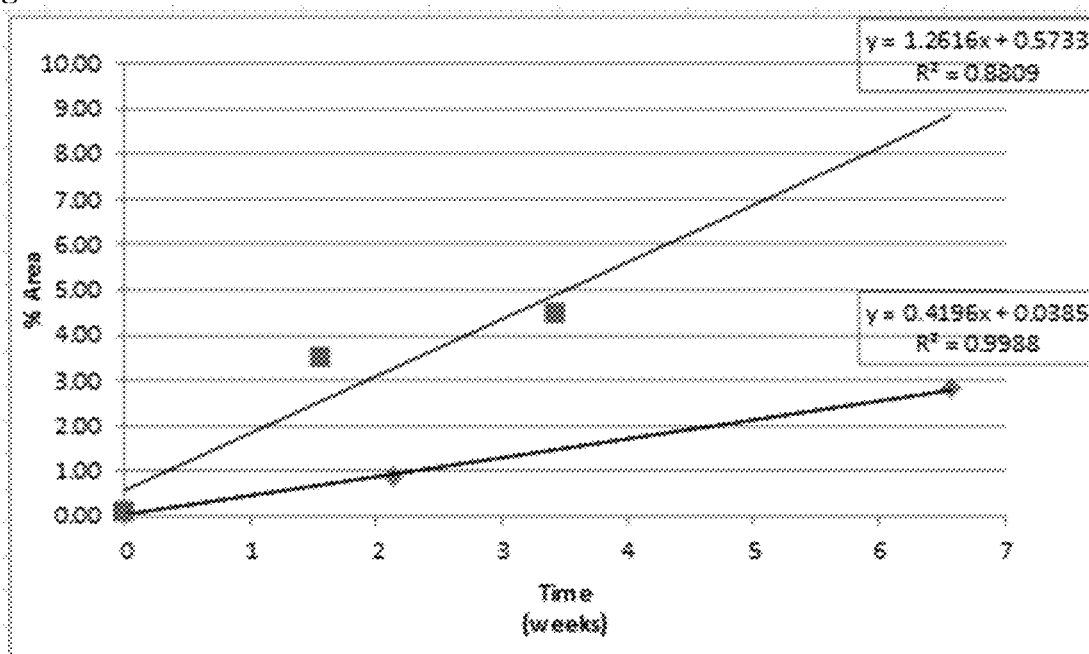


Fig. 1C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	1.24844 at 40C		0.4	0.1
rate	0.60617 at 30C		0.8	0.2
rate	0.41477 at 25C		1.2	0.3
rate	0.07932 at 2-8C		6.3	1.6
rate	0.00694 at -20C		N/A	N/A

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Fig. 2A

Weeks						
	Temp (°C)	0	1	2.142857	4	6.571429
T1	25	0.08		0.9		2.8
T2	60	0.08	10.5		11.3	

Fig. 2B

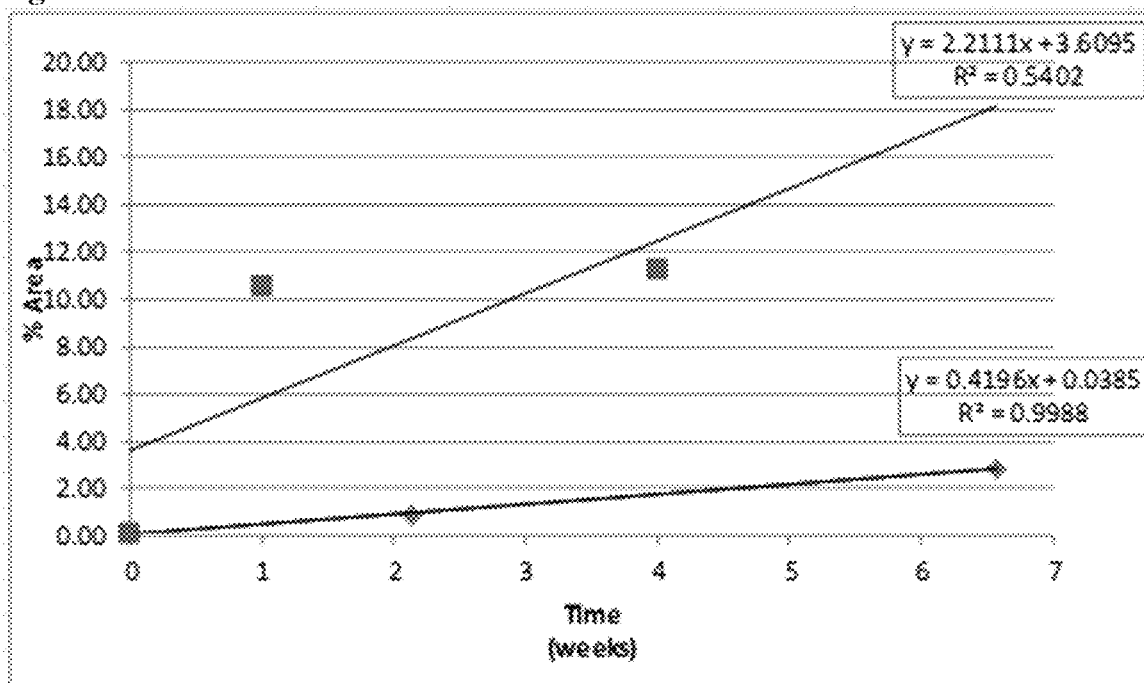


Fig. 2C

Formulation:		Average of Analysts	
Stability Prediction:		RRT 0.87	
	spec limit:	0.50	% (not more than)
			shelf life
		weeks	months
rate	0.88876 at 40C	0.6	0.1
rate	0.54051 at 30C	0.9	0.2
rate	0.41627 at 25C	1.2	0.3
rate	0.13331 at 2-8C	3.8	0.9
rate	0.02493 at -20C	N/A	N/A

Fig. 3

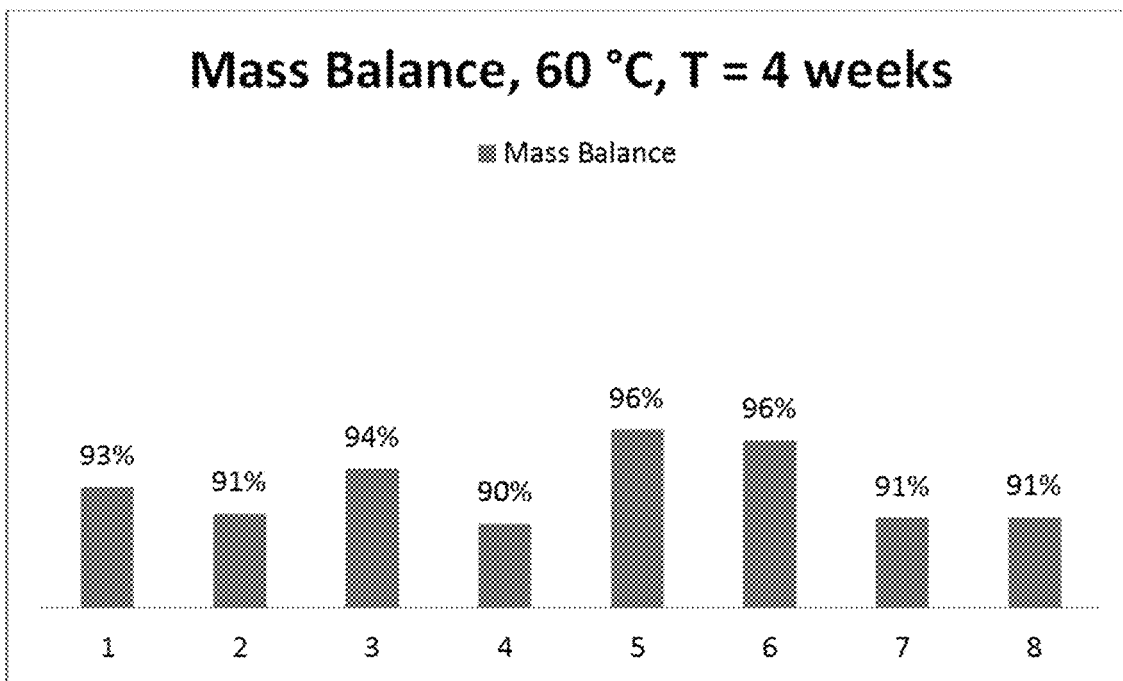


Fig. 4

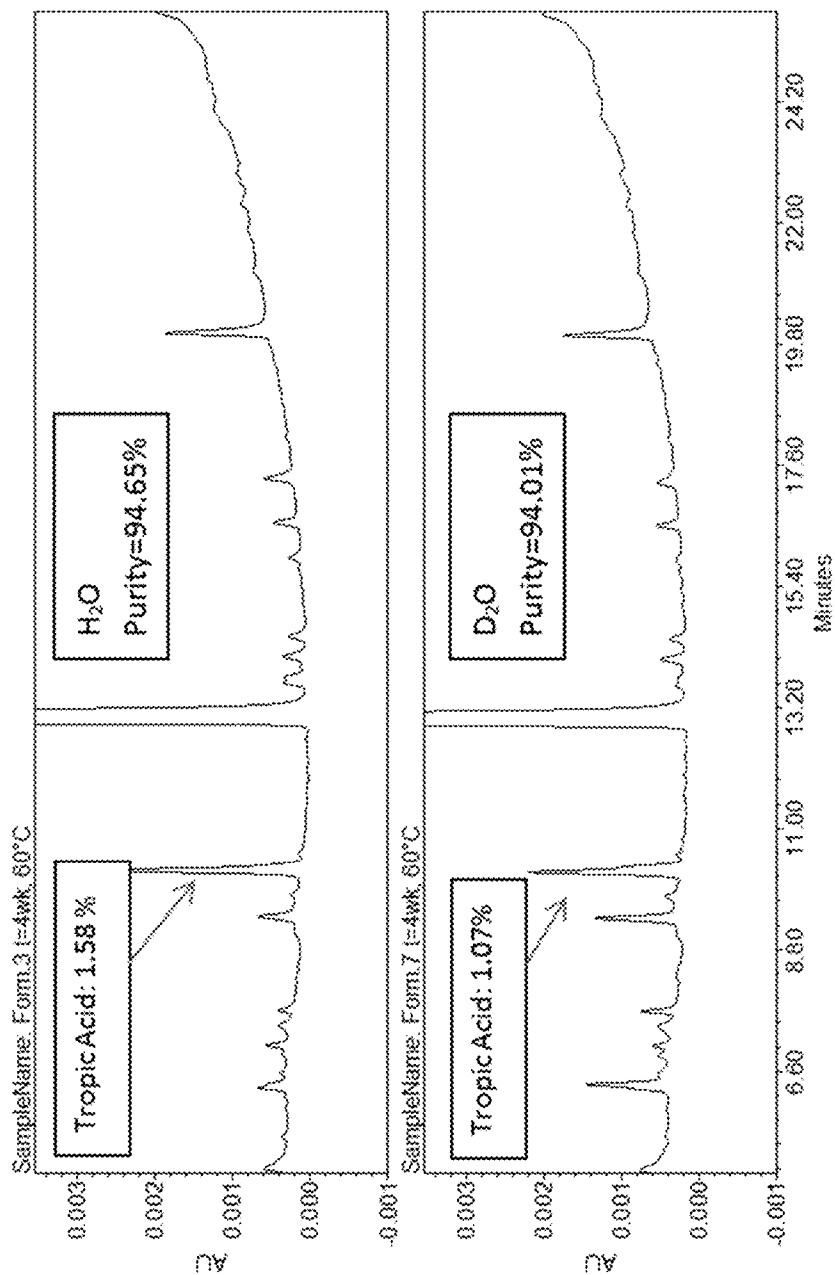


Fig. 5

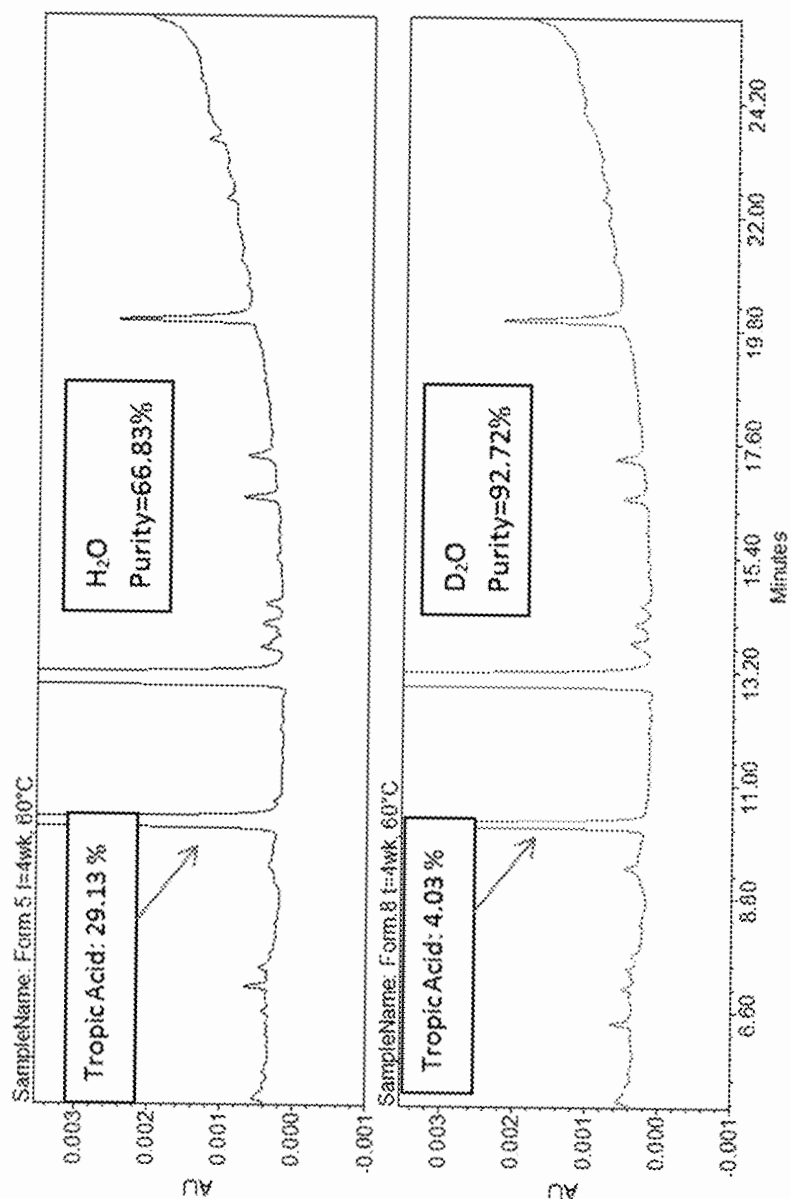


Fig. 6

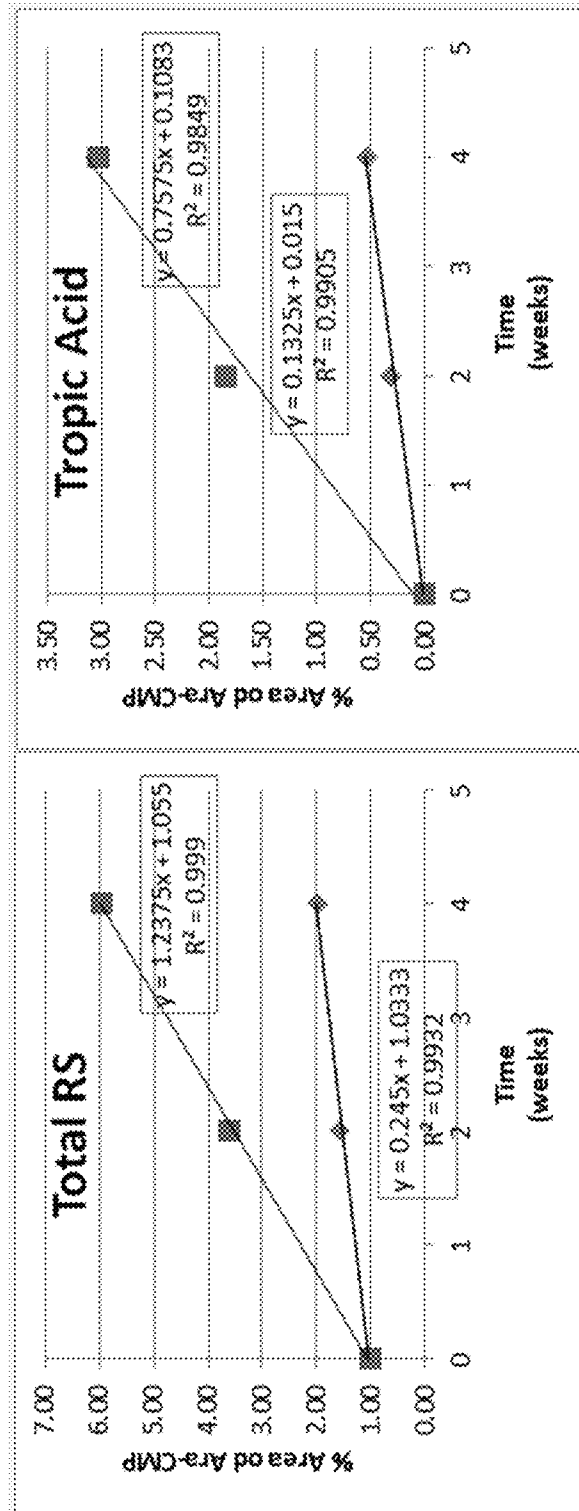


Fig. 7

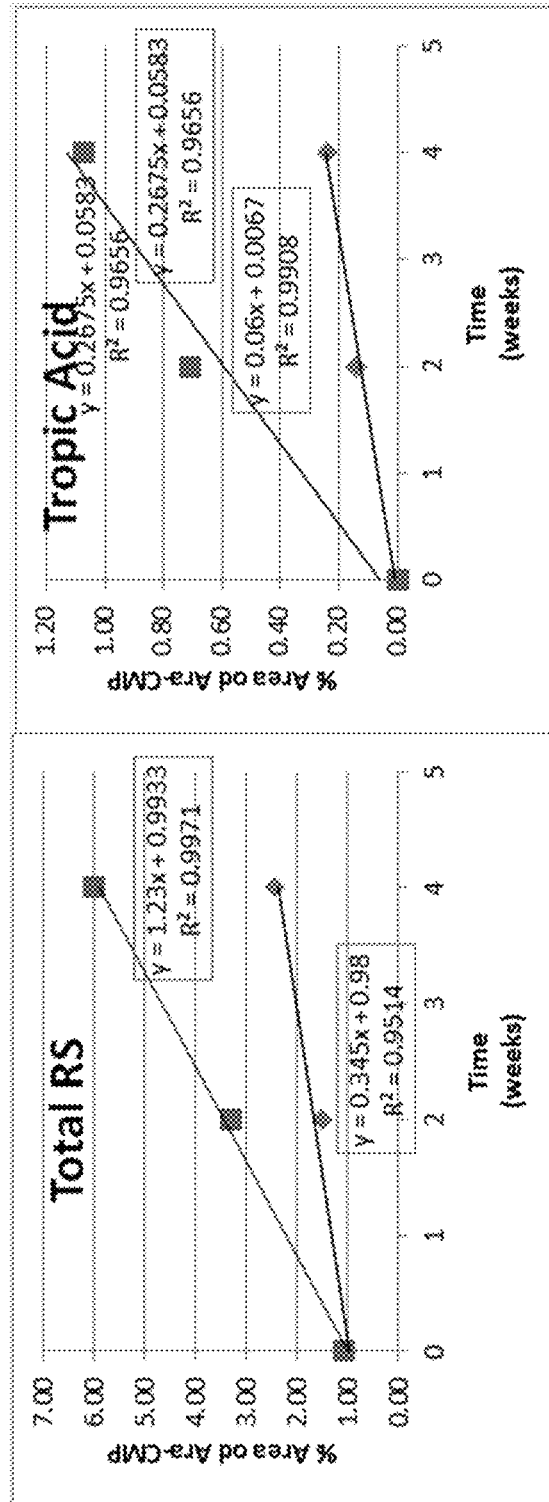


Fig. 8

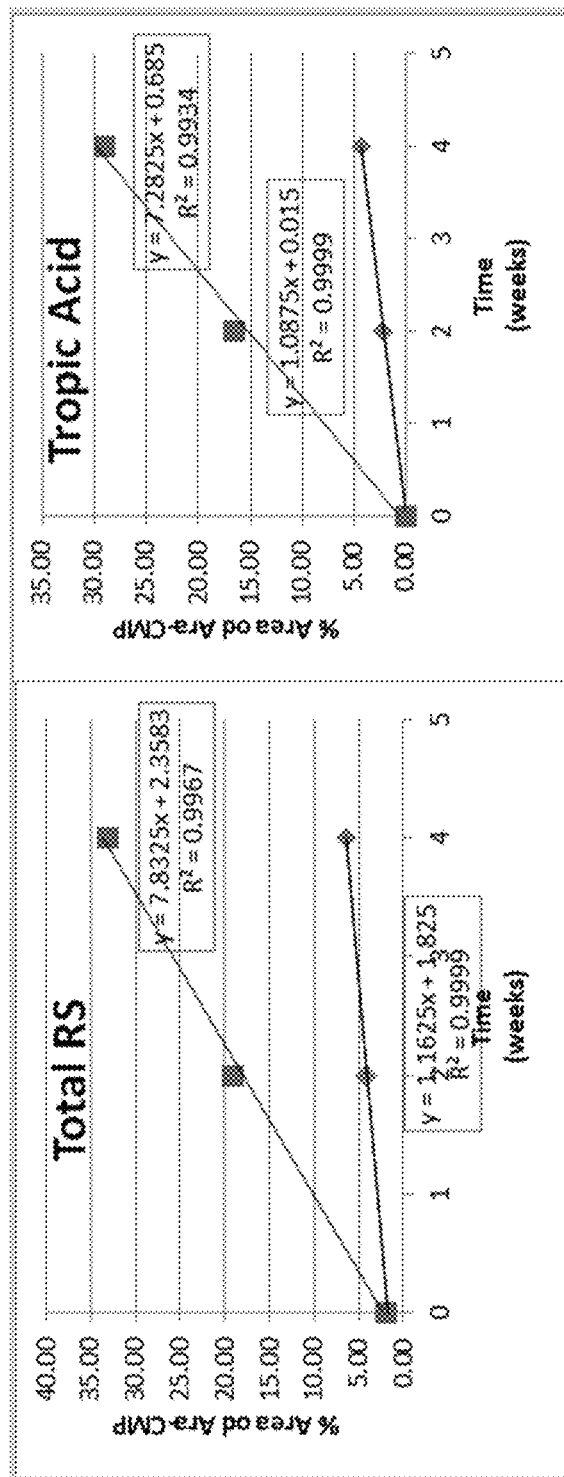


Fig. 9

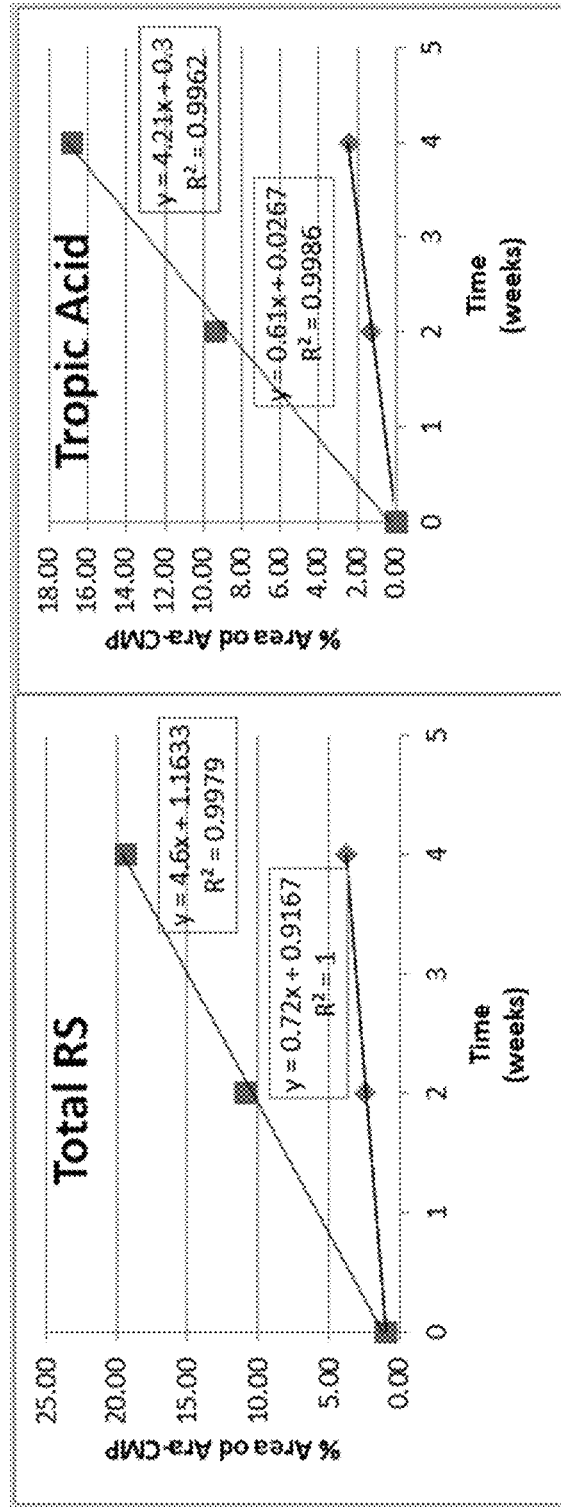


Fig. 10

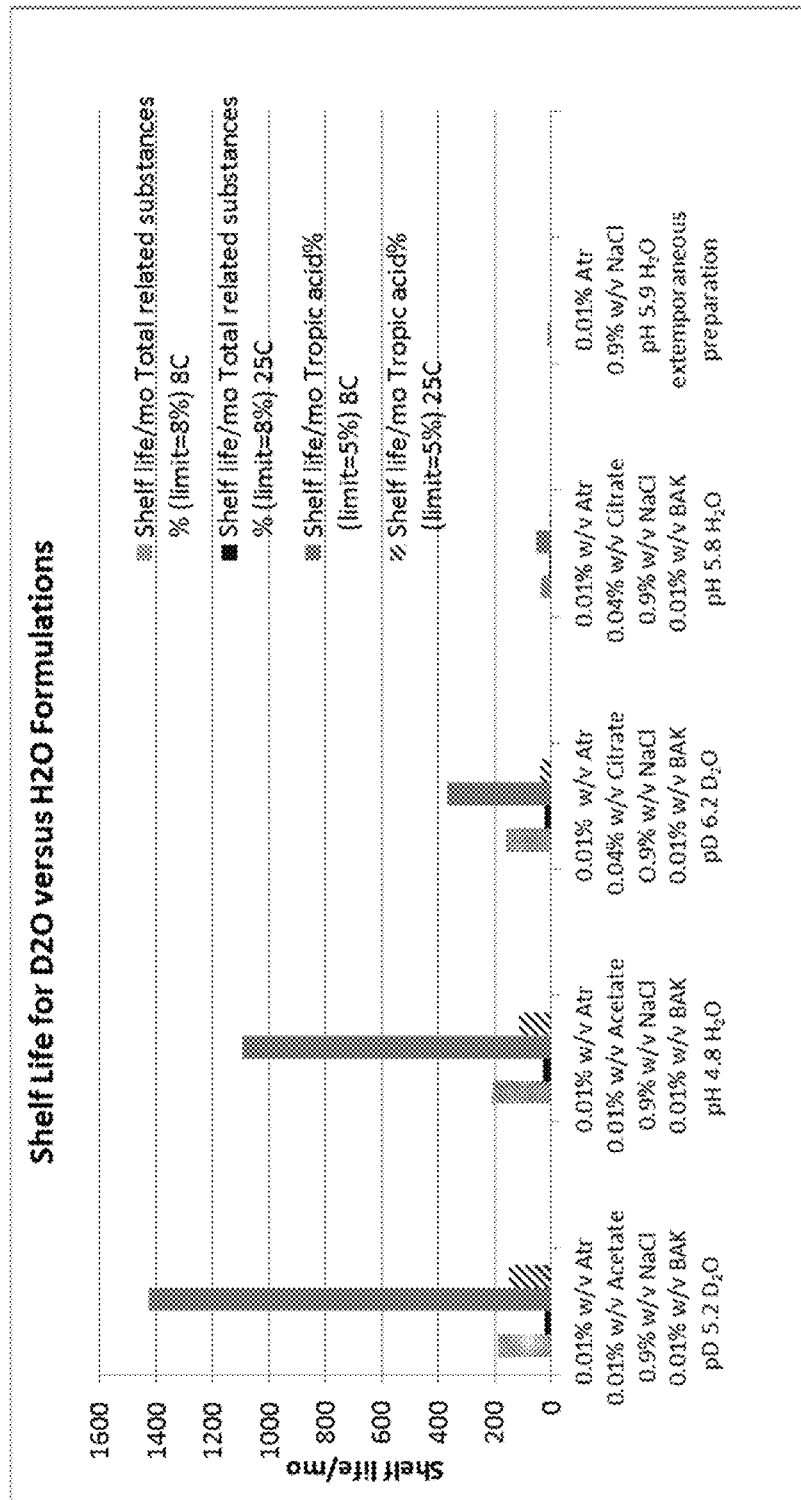


Fig. 11A

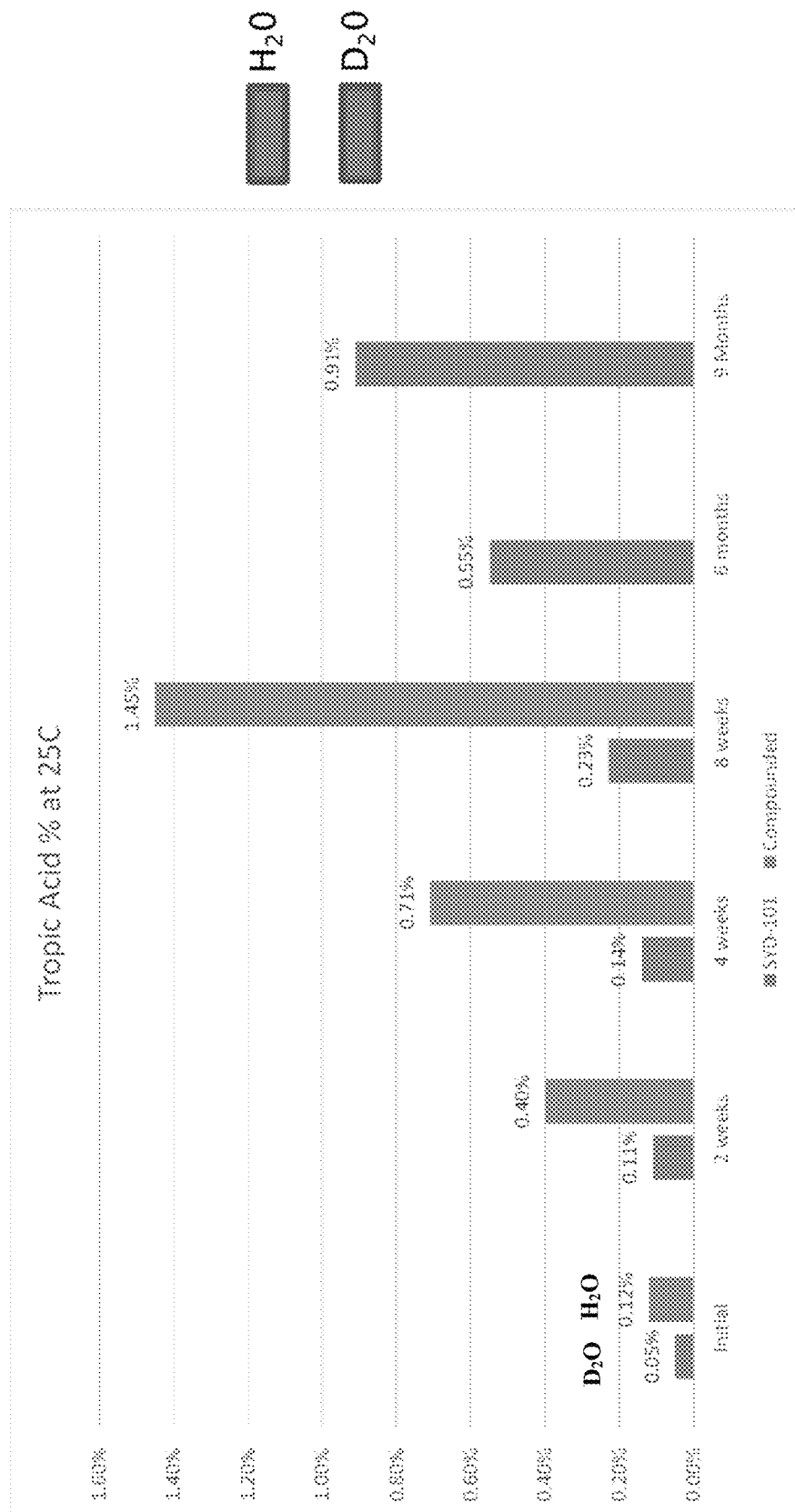
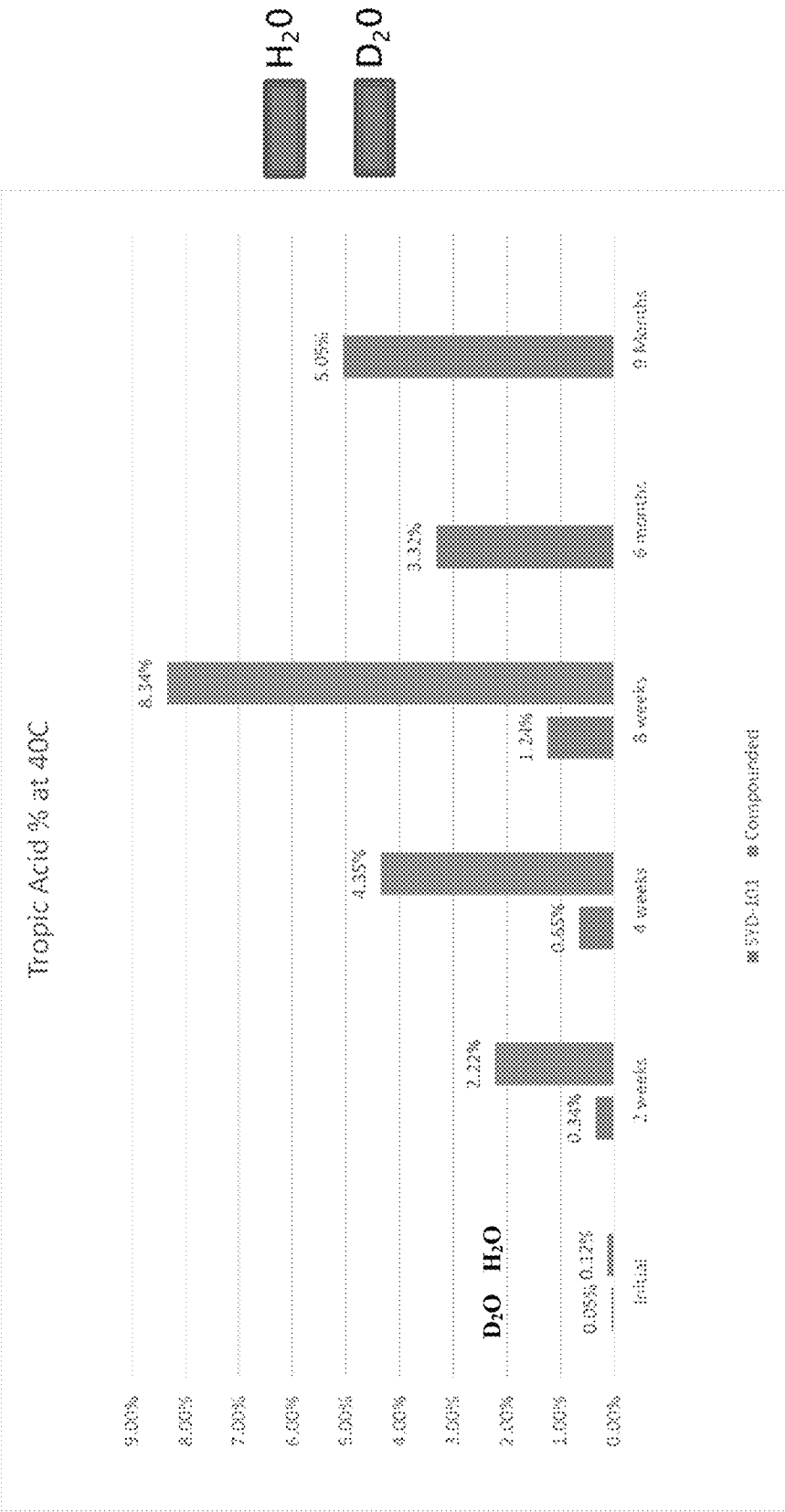


Fig. 11B



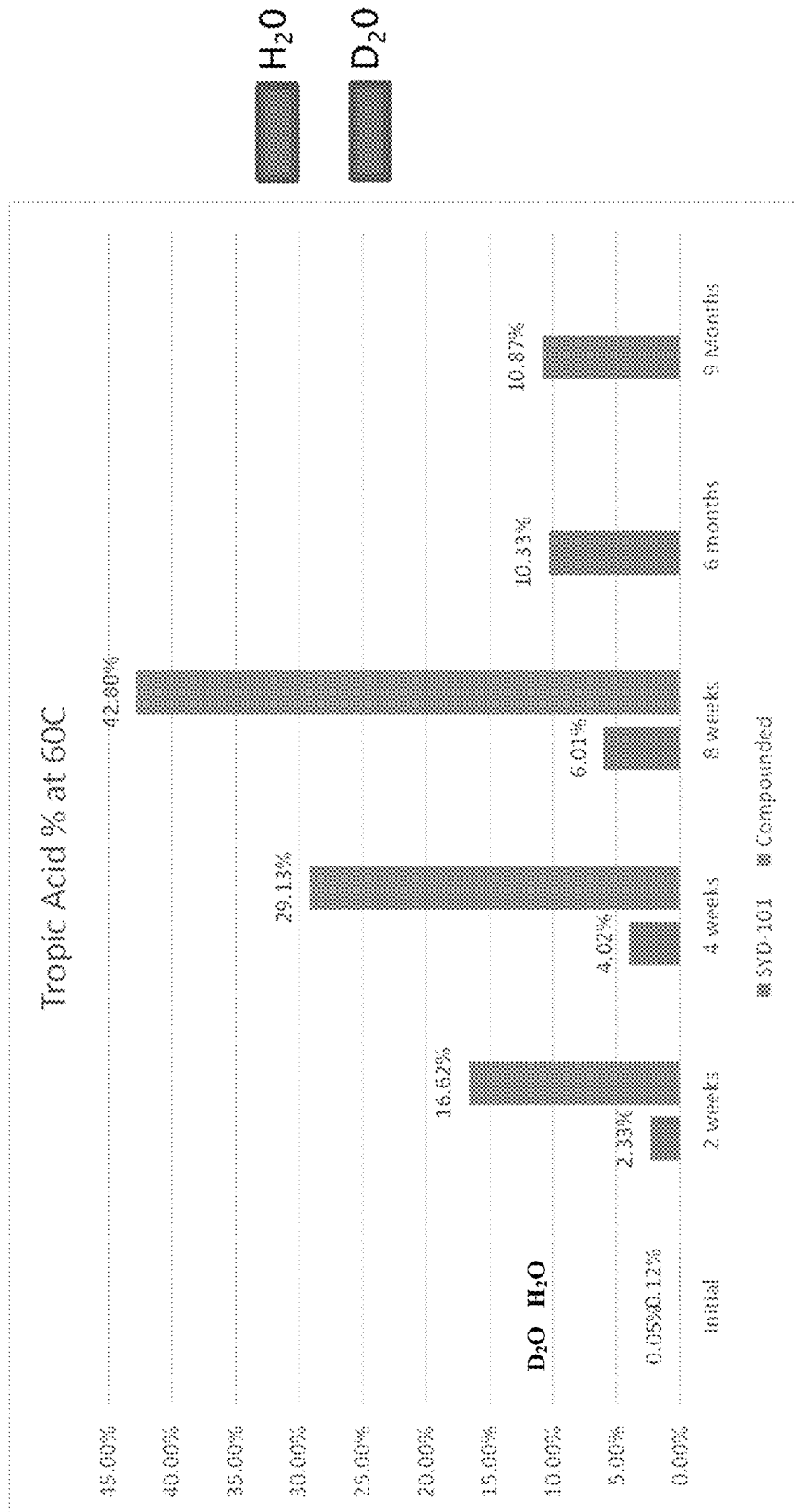
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Fig. 11C



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OPHTHALMIC COMPOSITION**CROSS-REFERENCE**

This application is a continuation of U.S. application Ser. No. 16/677,538, filed Nov. 7, 2019, which is a continuation of U.S. application Ser. No. 15/568,381, filed Oct. 20, 2017, which is a § 371 U.S. National Stage Application of International Application No. PCT/US2016/029222, filed Apr. 25, 2016, which is a continuation in part of International Application No. PCT/US2015/037249, filed Jun. 23, 2015, which is a continuation in part of U.S. application Ser. No. 14/726,139, filed May 29, 2015, now U.S. Pat. No. 9,421,199, issued Aug. 23, 2016, which claims the benefit of U.S. Provisional Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2015/037249 claims the benefit of U.S. Provisional Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2016/029222 claims benefit of U.S. Provisional Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2016/029222 is a continuation in part of U.S. application Ser. No. 14/726,139, filed May 29, 2015, now U.S. Pat. No. 9,421,199, issued Jun. 23, 2016, all of which their entire contents are fully incorporated herein by reference.

BACKGROUND OF THE DISCLOSURE

Pharmaceutical formulations have an expiration date which is based on the degradation of the active ingredient.

SUMMARY OF THE DISCLOSURE

Provided herein are ophthalmic compositions. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.

In some embodiments, provided herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist does not extend singlet oxygen lifetime.

In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the muscarinic antagonist quenches photogenerated singlet oxygen species in the composition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less

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than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.

In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.8, less than about 7.7, less than about 7.6, less than about 7.5, less than about 7.4, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.9, less than about 6.8, less than about 6.7, less than about 6.6, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6.

In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. As described in this disclosure, the percentage of the ophthalmic agent in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. As described in this disclosure, the potency of the ophthalmic agent in the composition after storage is based on the potency of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some embodiments, the storage condition has a storage temperature of about 25° C. In some embodiments, the storage condition has a storage temperature of about 40° C. In some embodiments, the storage condition has a storage temperature of about 60° C.

In some embodiments, the storage condition has a relative humidity of about 60%. In some embodiments, the storage condition has a relative humidity of about 75%.

In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period

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of time under storage condition. In some embodiments, the composition comprises less than 2.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid. As described in this disclosure, the percentage of the primary degradant in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the composition is in a form of an aqueous solution.

In some embodiments, the composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some embodiments, the composition is stored in a plastic container. In some embodiments, the material of the

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plastic container comprises low-density polyethylene (LDPE). In some cases, the material of the plastic container comprises polypropylene.

In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

In some embodiments, the composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, NaOD, CD_3COOD , or $\text{C}_6\text{D}_8\text{O}_7$.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the ophthalmically acceptable carrier further comprises at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

In some embodiments, the ophthalmic composition comprises one of: less than 60% of H_2O , less than 55% of H_2O , less than 50% of H_2O , less than 45% of H_2O , less than 40% of H_2O , less than 35% of H_2O , less than 30% of H_2O , less than 25% of H_2O , less than 20% of H_2O , less than 15% of H_2O , or less than 10% of H_2O .

In some embodiments, the ophthalmic composition comprises one of: less than 5% of H_2O , less than 4% of H_2O , less than 3% of H_2O , less than 2% of H_2O , less than 1% of H_2O , less than 0.5% of H_2O , less than 0.1% of H_2O , or 0% of H_2O .

In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use.

In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

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In some embodiments, the ophthalmic composition does not comprise water-hydrolyzable derivatives of α -amino or α -hydroxy-carboxylic acids.

In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.

In some embodiments, the ophthalmic composition is a solution.

In some embodiments, disclosed herein is a method of treating an ophthalmic disorder comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of treating an ophthalmic disorder, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, disclosed herein is a method of arresting myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. Also described herein is a method of preventing myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of arresting or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years,

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or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, disclosed herein is an ophthalmic solution that comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic solution has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the ophthalmic solution comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O. In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years. In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %. In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

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In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or atropine sulfate.

In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

In some embodiments, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some embodiments, the storage condition has a storage temperature of one of: about 25° C., about 40° C., or about 60° C. In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C.

In some embodiments, the storage condition has a relative humidity of about 60% or about 75%.

In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate,

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potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some embodiments, the ophthalmic composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE).

In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some embodiments, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

In some embodiments, the ophthalmic composition comprises one of: less than 60% of D₂O, less than 55% of D₂O, less than 50% of D₂O, less than 45% of D₂O, less than 40% of D₂O, less than 35% of D₂O, less than 30% of D₂O, less than 25% of D₂O, less than 20% of D₂O, less than 15% of D₂O, or less than 10% of D₂O.

In some embodiments, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% of D₂O. In some embodiments, ophthalmic composition is essentially free of D₂O.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

Other features and technical effects of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

FIG. 1A-FIG. 1C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT

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0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 40° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

FIG. 2A-FIG. 2C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 60° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

FIG. 3 illustrates mass balance at 4 weeks and at 60° C. condition for atropine sulfate formulations disclosed in Example 9.

FIG. 4 illustrates atropine sulfate (0.010%) formulation stability in acetic acid. The atropine sulfate formulation is formulated with acetic acid and either with H₂O (top panel, Formulation 3) or D₂O (bottom panel, Formulation 7). Formulation 3 has a pH of 4.8 and Formulation 7 has a pD of 5.2. Both formulations are stored at 60° C. for 4 weeks prior to analysis.

FIG. 5 illustrates atropine sulfate (0.01%) formulation stability in citric acid. The atropine sulfate formulation is formulated with citric acid and either with H₂O (top panel, Formulation 5) or D₂O (bottom panel, Formulation 8). Formulation 5 has a pH of 5.8 and Formulation 8 has a pD of 6.2. Both formulations are stored at 60° C. for 4 weeks prior to analysis.

FIG. 6 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 4) at pH 5.8 in H₂O.

FIG. 7 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 7) at pD 5.2 in D₂O.

FIG. 8 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 5) at pH 5.8 in H₂O.

FIG. 9 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 6) at pH 5.8 in H₂O.

FIG. 10 illustrates estimated shelf lives for D₂O and H₂O formulations disclosed in Examples 11 and 12.

FIG. 11A-FIG. 11C illustrate stability of atropine sulfate formulation 8 in H₂O and D₂O under three storage conditions.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure recognizes that there is a need for a stabilized ophthalmic composition with extended shelf life upon storage. The present disclosure also recognizes that there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active agents. The present disclosure further recognizes that there is a need for an ophthalmic composition that provides convenient and effective delivery of a muscarinic antagonist such as atropine in the eye of a patient.

The present disclosure recognizes that muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people. The present disclosure also recognizes the effects of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) on reduction of axial elongation and myopia in visually impaired chick eyes, and on ocular growth and muscarinic cholinergic receptors in young rhesus monkeys.

In addition, the present disclosure recognizes that systemic absorption of muscarinic antagonist (e.g. atropine)

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sometimes leads to undesirable side effect, and that localized delivery of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) reduces or prevents the aforementioned systemic exposure.

Further, the present disclosure recognizes that some liquid muscarinic antagonist (e.g. atropine) compositions are formulated at a relatively lower pH range (e.g. less than 4.5) for stability of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). For some individuals, the lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye, which is prevented or alleviated by formulating muscarinic antagonist (e.g. atropine) compositions at higher pH ranges. For some individuals, the lower pH in some instances elicits a tear response which reduces the absorption of the drug in the eye and therefore the effectiveness.

Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present stability challenges that are less so in higher concentrations (e.g. 0.1-1%). Without wishing to be bound by any particular theory, it is contemplated that the some muscarinic antagonist (e.g. atropine) contributes to the stability of an ophthalmic composition, such as an aqueous solution. For example, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the pH or pD of the ophthalmic composition, such as with the muscarinic antagonist acting as a buffering agent. Furthermore, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the interaction between the muscarinic antagonist and other ingredients of the ophthalmic composition, which in turn affects the stability of the ophthalmic composition.

Finally, the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions. In some cases, the deuterated water is a weak acid as compared to H₂O, as such deuterated water comprises a lower concentration of the reactive species (e.g., —OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H₂O. In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

Myopia, axial elongation of the eye, affects a large proportion of the population. The onset of myopia is generally during the grade school years and progresses until growth of the eye is completed. The present disclosure recognizes the importance of compositions and treatments for preventing or arresting the development of myopia, especially compositions and treatments that allow convenient administration, reduce potential side effects, has suitable stability, and/or provide relatively consistent therapeutic effects.

Ophthalmic Muscarinic Antagonist Composition

Provided herein is an ophthalmic composition containing low concentrations of an ophthalmic agent. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. In some instances, the ophthalmic agent is a muscarinic antagonist.

Provided herein is an ophthalmic composition containing low concentrations of a muscarinic antagonist. In some

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embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the muscarinic antagonist is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the ophthalmic composition comprise a muscarinic antagonist selected from atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, or homatropine.

In some embodiments, the ophthalmic composition comprise two or more muscarinic antagonists in which the two or more muscarinic antagonists comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or any combination thereof.

In some embodiments, the ophthalmic composition comprises one or more muscarinic antagonist in combination with one or more sympathetic agonists. In some embodiments, the sympathetic agonist is selected from phenylephrine or hydroxyamphetamine. In some embodiments, the ophthalmic composition comprises one or more of muscarinic antagonist: atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combi-

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nation with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

Provided herein is an ophthalmic composition containing low concentrations of atropine or its pharmaceutically acceptable salts. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of atropine or its pharmaceutically acceptable salts for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

Provided herein is an ophthalmic composition containing low concentrations of atropine sulfate. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of atropine sulfate for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

The present disclosure further recognizes that the clinical use of atropine as a therapy has been limited due to its ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation. Without wishing to be bound by any particular theory, it is contemplated that the limited use of atropine against myopia development, include its ocular side effects, is attributable to the concentration of atropine used in known ophthalmic formulations (e.g. 1 wt % or higher).

The present disclosure further recognizes the challenges present in formulation of compositions that contain low concentrations, especially very low concentrations (e.g. from about 0.001 wt % to about 0.5 wt %), of ophthalmic agents, such as muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). In particular, pharmaceutical compositions with ophthalmic agent at such low concentrations are difficult to maintain dose-to-dose uniformity in term of ophthalmic agent content and/or distribution.

In some aspects, described herein are formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water. In some aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

In additional aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water has a lowered buffering capacity. In such instances, the lowered buffering capacity of the ophthalmic formulations or solutions when administered into the eye allows the ophthalmic formulation or solution to reach physiological pH at a faster rate than compared to an equivalent ophthalmic formulation or solution formulated in H₂O.

In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that does not have a dose-to-dose variation. In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

In other aspects, described herein include formulating the ophthalmic composition as an ophthalmic gel or an ophthalmic ointment. For example, some ophthalmic gel or an

[illegible]

nist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 97% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 98% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 99% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition.

[illegible]

In some embodiments, the extended period of time is at least 1 week. In some embodiments, the extended period of time is at least 2 weeks. In some embodiments, the extended period of time is at least 3 weeks. In some embodiments, the extended period of time is at least 1 month. In some embodiments, the extended period of time is at least 2 months. In some embodiments, the extended period of time is at least 3 months. In some embodiments, the extended period of time is at least 4 months. In some embodiments, the extended period of time is at least 5 months. In some embodiments, the extended period of time is at least 6 months. In some embodiments, the extended period of time

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is at least 7 months. In some embodiments, the extended period of time is at least 8 months. In some embodiments, the extended period of time is at least 9 months. In some embodiments, the extended period of time is at least 10 months. In some embodiments, the extended period of time is at least 11 months. In some embodiments, the extended period of time is at least 12 months (i.e. 1 year). In some embodiments, the extended period of time is at least 18 months (i.e. 1.5 years). In some embodiments, the extended period of time is at least 24 months (i.e. 2 years). In some embodiments, the extended period of time is at least 36 months (i.e. 3 years). In some embodiments, the extended period of time is at least 3 years. In some embodiments, the extended period of time is at least 5 years, or more.

In some embodiments, the temperature of the storage condition is between about 20° C. and about 70° C. In some embodiments, the temperature of the storage condition is between about 25° C. and about 65° C., about 30° C. and about 60° C., about 35° C. and about 55° C., or about 40° C. and about 50° C. In some embodiments, the temperature of the storage condition is about 25° C. In some embodiments, the temperature of the storage condition is about 40° C. In some embodiments, the temperature of the storage condition is about 60° C.

In some embodiments, the relative humidity of the storage condition is between about 50% and about 80%, or between about 60% and about 75%. In some embodiments, the relative humidity of the storage condition is about 60%. In some embodiments, the relative humidity of the storage condition is about 75%.

In some embodiments, the composition comprises less than 60% of H₂O. In some embodiments, the composition comprises less than 55% of H₂O. In some embodiments, the composition comprises less than 50% of H₂O. In some embodiments, the composition comprises less than 45% of H₂O. In some embodiments, the composition comprises less than 40% of H₂O. In some embodiments, the composition comprises less than 35% of H₂O. In some embodiments, the composition comprises less than 30% of H₂O. In some embodiments, the composition comprises less than 25% of H₂O. In some embodiments, the composition comprises less than 20% of H₂O. In some embodiments, the composition comprises less than 15% of H₂O. In some embodiments, the composition comprises less than 10% of H₂O.

In some embodiments, the composition comprises from less than 5% of H₂O to 0% of H₂O. In some embodiments, the composition comprises less than 5% of H₂O. In some embodiments, the composition comprises less than 4.5% of H₂O. In some embodiments, the composition comprises less than 4% of H₂O. In some embodiments, the composition comprises less than 3.5% of H₂O. In some embodiments, the composition comprises less than 3% of H₂O. In some embodiments, the composition comprises less than 2.5% of H₂O. In some embodiments, the composition comprises less than 2% of H₂O. In some embodiments, the composition comprises less than 1.5% of H₂O. In some embodiments, the composition comprises less than 1% of H₂O. In some embodiments, the composition comprises less than 0.5% of H₂O. In some embodiments, the composition comprises less than 0.4% of H₂O. In some embodiments, the composition comprises less than 0.3% of H₂O. In some embodiments, the composition comprises less than 0.2% of H₂O. In some embodiments, the composition comprises less than 0.1% of H₂O. In some embodiments, the composition comprises 0% of H₂O.

In some embodiments, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about

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5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments, the composition has a pD of less than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4.

In some embodiments, the composition comprising deuterated water has a lowered buffering capacity than an equivalent composition comprising H₂O. As described elsewhere herein, in some embodiments, the lowered buffering capacity allows the composition comprising deuterated water to normalize to physiological pH at a faster rate than a composition comprising H₂O. In some embodiments, the lowered buffering capacity allows the composition to induce less tear reflex than an equivalent composition comprising H₂O.

In some instances, the composition comprising deuterated water stabilizes muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O

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aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid.

In some embodiments, the primary degradant is an early eluting related substance at RRT of 0.87-0.89 according to the UPLC method described herein (Table 10). In some instances, the early eluting related substance is referred to as RRT 0.87-0.89. In some embodiments, the primary degradant is RRT 0.87-0.89.

In some embodiments, the composition does not stabilize singlet oxygen upon irradiation with UV. In some cases, one or more of muscarinic antagonists described herein does not extend singlet oxygen lifetime. In some cases, one or more of muscarinic antagonists described herein is a radical scavenger, which quenches photogenerated singlet oxygen species within the composition. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, homatropine, scopolamine or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine or atropine sul-

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fate. In some instances, a composition comprising atropine or atropine sulfate does not stabilize singlet oxygen upon irradiation with UV. In some instances, a composition comprising atropine or atropine sulfate quenches photogenerated singlet oxygen species present in the composition.

Ophthalmic Muscarinic Antagonist Concentration

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.050%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate. As described herein, the ophthalmic agent includes optically pure stereoisomers, optically enriched stereoisomers, and a racemic mixture of stereoisomers. For example, some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a racemic mixture of D- and L-isomers; and some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a optically enriched in favor of the more ophthalmically active L-isomer.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.045%, between about 0.005% to about 0.045%, between about 0.010% to about 0.045%, between about 0.015% to about 0.045%, between about 0.020% to about 0.045%, between about 0.025% to about 0.045%, between about 0.030% to about 0.045%, between about 0.035% to about 0.045%, or between about 0.040% to about 0.045% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.040%, between about 0.005% to about 0.040%, between about 0.010% to about 0.040%, between about 0.015% to about 0.040%, between about 0.020% to about 0.040%, between about 0.025% to about 0.040%, between about 0.030% to about 0.040%, between about 0.035% to about 0.040% of the active ingredient, or phar-

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maceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.035%, between about 0.005% to about 0.035%, between about 0.010% to about 0.035%, between about 0.015% to about 0.035%, between about 0.020% to about 0.035%, between about 0.025% to about 0.035%, or between about 0.030% to about 0.035% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.030%, between about 0.005% to about 0.030%, between about 0.010% to about 0.030%, between about 0.015% to about 0.030%, between about 0.020% to about 0.030%, or between about 0.025% to about 0.030% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.025%, between about 0.005% to about 0.025%, between about 0.010% to about 0.025%, between about 0.015% to about 0.025%, or between about 0.020% to about 0.025% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.020%, between about 0.005% to about 0.020%, between about 0.010% to about 0.020%, or between about 0.015% to about 0.020% of the active ingredient, or pharmaceutically acceptable prodrug or salt

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thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.015%, between about 0.005% to about 0.015%, or between about 0.010% to about 0.015% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.010%, between about 0.005% to about 0.010%, or between about 0.008% to about 0.010% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

Without wishing to be bound by any particular theory, it is contemplated herein that the low concentration of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate) in the disclosed ophthalmic composition provides sufficient and consistent therapeutic benefits to an individual in need thereof, while reducing or avoiding the ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation that are associated with ophthalmic formulations containing higher concentrations of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate).

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Aqueous Solution Stability

In some embodiments, the composition described herein comprises a buffer. In some embodiments, a buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof. In some embodiments, the composition described herein comprises buffer comprising deuterated water. In some embodiments, a deuterated buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof, formulated in deuterated water.

In some instances, borates include boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof in some cases, borates include boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

As used herein, the term polyol includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. In some embodiments, the polyols is linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. In some instances, examples of polyol include: sugars, sugar alcohols, sugar acids and uronic acids. In some cases, polyols include, but are not limited to: mannitol, glycerin, xylitol and sorbitol.

In some embodiments, phosphate buffering agents include phosphoric acid; alkali metal phosphates such as disodium hydrogen phosphate, sodium dihydrogen phosphate, trisodium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, and tripotassium phosphate; alkaline earth metal phosphates such as calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, monomagnesium phosphate, dimagnesium phosphate (magnesium hydrogen phosphate), and trimagnesium phosphate; ammonium phosphates such as diammonium hydrogen phosphate and ammonium dihydrogen phosphate; or a combination thereof. In some instances, the phosphate buffering agent is an anhydride. In some instances, the phosphate buffering agent is a hydrate.

In some embodiments, borate-polyol complexes include those described in U.S. Pat. No. 6,503,497. In some instances, the borate-polyol complexes comprise borates in an amount of from about 0.01 to about 2.0% w/v, and one or more polyols in an amount of from about 0.01% to about 5.0% w/v.

In some cases, citrate buffering agents include citric acid and sodium citrate.

In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

In some cases, organic buffering agents include Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), N-(2-Acetamido)iminodiacetic acid, N-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-N,N'-bis(2-ethanesulfonic acid (PIPES), N-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β -Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), cholamine chloride, 3-(N-morpholino)propanesulfonic acid (MOPS), N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid

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(BES), 2-[(2-Hydroxy-1,1-bis(hydroxymethyl)ethyl)amino]ethanesulfonic acid (TES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 3-(N,N-Bis[2-hydroxyethyl]amino)-2-hydroxypropanesulfonic acid (DIPSO), acetamidoglycine, 3-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propanyl]amino]-2-hydroxy-1-propanesulfonic acid (TAPSO), piperazine-1,4-bis (2-hydroxypropanesulphonic acid) (POPSO), 4-(2-hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate (HEPPSO), 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid (HEPPS), tricine, glycineamide, bicine or N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; and diethanolamine (DEA).

In some cases, amino acid buffering agents include taurine, aspartic acid and its salts (e.g., potassium salts, etc), E-aminocaproic acid, and the like.

In some instances, the composition described herein further comprises a tonicity adjusting agent. Tonicity adjusting agent is an agent introduced into a preparation such as an ophthalmic composition to reduce local irritation by preventing osmotic shock at the site of application. In some instances, buffer solution and/or a pD adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pD are considered as tonicity adjusting agents. In some cases, tonicity adjusting agents include various salts, such as halide salts of a monovalent cation. In some cases, tonicity adjusting agents include mannitol, sorbitol, dextrose, sucrose, urea, and glycerin. In some instances, suitable tonicity adjustors comprise sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.5% and about 2.0%. In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.7% and about 1.8%, about 0.8% and about 1.5%, or about 1% and about 1.3%. In some instances, the concentration of the tonicity adjusting agent is about 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, or 1.9%. In some cases, the percentage is a weight percentage.

In some cases, the composition described herein further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent used is an acid or a base. In some embodiments, the base is oxides, hydroxides, carbonates, bicarbonates and the likes. In some instances, the oxides are metal oxides such as calcium oxide, magnesium oxide and the likes; hydroxides are of alkali metals and alkaline earth metals such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the likes or their deuterated equivalents, and carbonates are sodium carbonate, sodium bicarbonates, potassium bicarbonates and the likes. In some instances, the acid is mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric acid and the likes or their deuterated equivalents. In some instances, the pD adjusting agent includes, but is not limited to, acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agent comprises DCl and NaOD.

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about 6.4. In some embodiments, the composition has an initial pD of about 6.3. In some embodiments, the composition has an initial pD of about 6.2. In some embodiments, the composition has an initial pD of about 6.1. In some embodiments, the composition has an initial pD of about 6. In some embodiments, the composition has an initial pD of about 5.9. In some embodiments, the composition has an initial pD of about 5.8. In some embodiments, the composition has an initial pD of about 5.7. In some embodiments, the composition has an initial pD of about 5.6. In some embodiments, the composition has an initial pD of about 5.5. In some embodiments, the composition has an initial pD of about 5.4. In some embodiments, the composition has an initial pD of about 5.3. In some embodiments, the composition has an initial pD of about 5.2. In some embodiments, the composition has an initial pD of about 5.1. In some embodiments, the composition has an initial pD of about 5. In some embodiments, the composition has an initial pD of about 4.9. In some embodiments, the composition has an initial pD of about 4.8. In some embodiments, the composition has an initial pD of about 4.7. In some embodiments, the composition has an initial pD of about 4.6. In some embodiments, the composition has an initial pD of about 4.5. In some embodiments, the composition has an initial pD of about 4.4. In some embodiments, the composition has an initial pD of about 4.3. In some embodiments, the composition has an initial pD of about 4.2. In some embodiments, the composition has an initial pD of about 4.1. In some embodiments, the composition has an initial pD of about 4.

In some embodiments, the pD of the composition described herein is associated with the stability of the composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a stable composition comprises a pD of less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than

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about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

As described elsewhere herein, in some instances, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., —OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., —OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the presence of deuterated water shifts the pKa of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quaternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

In some instances, the composition described herein further comprises a preservative. In some cases, a preservative

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is added at a concentration to a composition described herein to prevent the growth of or to destroy a microorganism introduced into the composition. In some instances, microorganisms refer to bacteria (e.g. *Proteus mirabilis*, *Serratia marcescens*), virus (e.g. Herpes simplex virus, herpes zoster virus), fungus (e.g. fungi from the genus *Fusarium*), yeast (e.g. *Candida albicans*), parasites (e.g. *Plasmodium* spp., *Gnathostoma* spp.), protozoan (e.g. *Giardia lamblia*), nematodes (e.g. *Onchocercus volvulus*), worm (e.g. *Dirofilaria immitis*), and/or amoeba (e.g. *Acanthamoeba*).

In some instances, the concentration of the preservative is between about 0.0001% and about 1%, about 0.001% and about 0.8%, about 0.004% and about 0.5%, about 0.008% and about 0.1%, and about 0.01% and about 0.08%. In some cases, the concentration of the preservatives is about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.008%, 0.009%, 0.009%, 0.01%, 0.015%, 0.02%, 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9% or 1.0%.

In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia (Alcon), poly quaternium-1, chlorobutanol, edetate disodium, and polyhexamethylene biguanide.

In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the material of the plastic container comprises high density polyethylene (HDPE), low density polyethylene (LDPE), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polypropylene (PP), polystyrene (PS), fluorine treated HDPE, post-consumer resin (PCR), K-resine (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the composition stored in a plastic container has a pD of between about 4 and about 8, about 4.5 and about 7.9, or about 4.9 and about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.8. In some embodiments, the composi-

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tion stored in a plastic container has a pD of less than about 5.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.

In some embodiments, the composition stored in a plastic container has a potency of at least 70% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 75% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 99% after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25° C., about 40° C., or about 60° C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

In some embodiments, the composition stored in a plastic container has a potency of at least 80% at a temperature of

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about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 85% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 90% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 93% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 95% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 97% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 98% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 99% at a temperature of about 25° C., about 40° C., or about 60° C.

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ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container

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comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

In some embodiments, the composition described herein is stored in a glass container. In some embodiments, the glass container is a glass vial, such as for example, a type I, type II or type III glass vial. In some embodiments, the glass container is a type I glass vial. In some embodiments, the type I glass vial is a borasilicate glass vial.

In some embodiments, the composition stored in a glass container has a pD of higher than about 7. In some embodiments, the composition stored in a glass container has a pD of higher than about 7.5. In some embodiments, the composition stored in a glass container has a pD of higher than about 8. In some embodiments, the composition stored in a glass container has a pD of higher than about 8.5. In some embodiments, the composition stored in a glass container has a pD of higher than about 9.

In some embodiments, the composition stored in a glass container has a potency of less than 60% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a glass container has a potency of less than 60% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

In some embodiments, the composition stored in a glass container is less stable than a composition stored in a plastic container.

In some embodiments, the composition is stored under in the dark. In some instances, the composition is stored in the presence of light. In some instances, the light is indoor light, room light, or sun light. In some instances, the composition is stable while stored in the presence of light.

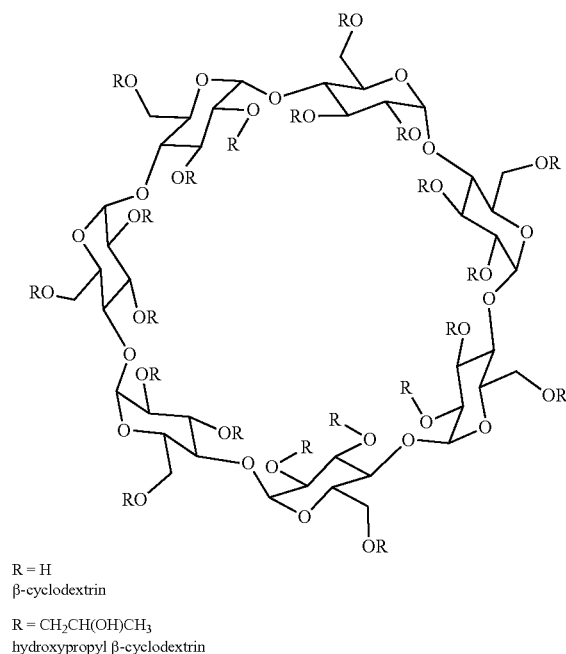
In some embodiments, the composition described herein is formulated as an aqueous solution. In some embodiments, the aqueous solution is a stable aqueous solution. In some instances, the aqueous solution is stored in a plastic container as described above. In some instances, the aqueous

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solution is not stored in a glass container. In some instances, the aqueous solution is stored in the dark. In some instances, the aqueous solution is stored in the presence of light. In some instances, the aqueous solution is stable in the presence of light.

In a specific embodiment, the ophthalmically acceptable formulations alternatively comprise a cyclodextrin. Cyclodextrins are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, referred to as α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin respectively. Cyclodextrins have a hydrophilic exterior, which enhances water-soluble, and a hydrophobic interior which forms a cavity. In an aqueous environment, hydrophobic portions of other molecules often enter the hydrophobic cavity of cyclodextrin to form inclusion compounds. Additionally, cyclodextrins are also capable of other types of nonbonding interactions with molecules that are not inside the hydrophobic cavity. Cyclodextrins have three free hydroxyl groups for each glucopyranose unit, or 18 hydroxyl groups on α -cyclodextrin, 21 hydroxyl groups on β -cyclodextrin, and 24 hydroxyl groups on γ -cyclodextrin. In some embodiments, one or more of these hydroxyl groups are reacted with any of a number of reagents to form a large variety of cyclodextrin derivatives, including hydroxypropyl ethers, sulfonates, and sulfoalkylethers. Shown below is the structure of β -cyclodextrin and the hydroxypropyl- β -cyclodextrin (HP β CD).



In some embodiments, the use of cyclodextrins in the pharmaceutical compositions described herein improves the solubility of the drug. Inclusion compounds are involved in many cases of enhanced solubility; however other interactions between cyclodextrins and insoluble compounds also improves solubility. Hydroxypropyl- β -cyclodextrin (HP β CD) is commercially available as a pyrogen free product. It is a nonhygroscopic white powder that readily dissolves in water. HP β CD is thermally stable and does not degrade at neutral pH. Thus, cyclodextrins improve the solubility of a therapeutic agent in a composition or formulation. Accordingly, in some embodiments, cyclodextrins are included to increase the solubility of the ophthalmically

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acceptable ophthalmic agents within the formulations described herein. In other embodiments, cyclodextrins in addition serve as controlled release excipients within the formulations described herein.

By way of example only, cyclodextrin derivatives for use include α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxyethyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, sulfated β -cyclodextrin, sulfated α -cyclodextrin, sulfobutyl ether β -cyclodextrin.

The concentration of the cyclodextrin used in the compositions and methods disclosed herein varies according to the physiochemical properties, pharmacokinetic properties, side effect or adverse events, formulation considerations, or other factors associated with the therapeutically ophthalmic agent, or a salt or prodrug thereof, or with the properties of other excipients in the composition. Thus, in certain circumstances, the concentration or amount of cyclodextrin used in accordance with the compositions and methods disclosed herein will vary, depending on the need. When used, the amount of cyclodextrins needed to increase solubility of the ophthalmic agent and/or function as a controlled release excipient in any of the formulations described herein is selected using the principles, examples, and teachings described herein.

Other stabilizers that are useful in the ophthalmically acceptable formulations disclosed herein include, for example, fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinyl pyrrolidones, polyvinyl ethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof.

In some embodiments, amide analogues of stabilizers are also used. In further embodiments, the chosen stabilizer changes the hydrophobicity of the formulation, improves the mixing of various components in the formulation, controls the moisture level in the formula, or controls the mobility of the phase.

In other embodiments, stabilizers are present in sufficient amounts to inhibit the degradation of the ophthalmic agent. Examples of such stabilizing agents, include, but are not limited to: glycerol, methionine, monothioglycerol, EDTA, ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate and other heparinoids, divalent cations such as magnesium and zinc, or combinations thereof.

Additional useful stabilization agents for ophthalmically acceptable formulations include one or more anti-aggregation additives to enhance stability of ophthalmic formulations by reducing the rate of protein aggregation. The anti-aggregation additive selected depends upon the nature of the conditions to which the ophthalmic agents, for example a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), are exposed. For example, certain formulations undergoing agitation and thermal stress require a different anti-aggregation additive than a formulation undergoing lyophilization and reconstitution. Useful anti-aggregation additives include, by way of example only, urea, guanidinium chloride, simple amino acids such as glycine or arginine, sugars, polyalcohols, polysorbates, polymers such as polyethylene glycol and dextrans, alkyl saccharides, such as alkyl glycoside, and surfactants.

Other useful formulations optionally include one or more ophthalmically acceptable antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid, methionine, sodium thiosulfate and sodium metabisulfite. In one embodiment,

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antioxidants are selected from metal chelating agents, thiol containing compounds and other general stabilizing agents.

Still other useful compositions include one or more ophthalmically acceptable surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

In some embodiments, the ophthalmically acceptable pharmaceutical formulations described herein are stable with respect to compound degradation (e.g. less than 30% degradation, less than 25% degradation, less than 20% degradation, less than 15% degradation, less than 10% degradation, less than 8% degradation, less than 5% degradation, less than 3% degradation, less than 2% degradation, or less than 5% degradation) over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 3 months, at least about 4 months, at least about 5 months, or at least about 6 months under storage conditions (e.g. room temperature). In other embodiments, the formulations described herein are stable with respect to compound degradation over a period of at least about 1 week. Also described herein are formulations that are stable with respect to compound degradation over a period of at least about 1 month.

In other embodiments, an additional surfactant (co-surfactant) and/or buffering agent is combined with one or more of the pharmaceutically acceptable vehicles previously described herein so that the surfactant and/or buffering agent maintains the product at an optimal pD for stability. Suitable co-surfactants include, but are not limited to: a) natural and synthetic lipophilic agents, e.g., phospholipids, cholesterol, and cholesterol fatty acid esters and derivatives thereof; b) nonionic surfactants, which include for example, polyoxyethylene fatty alcohol esters, sorbitan fatty acid esters (Spans), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20) and other Tweens, sorbitan esters, glycerol esters, e.g., Myrj and glycerol triacetate (triacetin), polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, polysorbate 80, poloxamers, poloxamines, polyoxyethylene castor oil derivatives (e.g., Cremophor® RH40, Cremphor A25, Cremphor A20, Cremophor® EL) and other Cremophors, sulfosuccinates, alkyl sulphates (SLS); PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprates (Labrasol), PEG-4 glyceryl caprylate/caprates (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 444/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprates; Brij® 700, ascorbyl-6-palmitate, stearylamine, sodium lauryl sulfate, polyoxethyleneglycerol triiricinoleate, and any combinations or mixtures thereof; c) anionic surfactants include, but are not limited to, calcium carboxymethylcellulose, sodium carboxymethylcellulose, sodium sulfosuccinate, dioctyl, sodium alginate, alkyl polyoxyethylene sulfates, sodium lauryl sulfate, triethanolamine stearate, potassium laurate, bile salts, and any combinations or mixtures thereof;

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and d) cationic surfactants such as cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride.

In a further embodiment, when one or more co-surfactants are utilized in the ophthalmically acceptable formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and is present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%.

In one embodiment, the surfactant has an HLB value of 0 to 20. In additional embodiments, the surfactant has an HLB value of 0 to 3, of 4 to 6, of 7 to 9, of 8 to 18, of 13 to 15, of 10 to 18.

pD

In some embodiments, the pD of a composition described herein is adjusted (e.g., by use of a buffer and/or a pD adjusting agent) to an ophthalmically compatible pD range of from about 4 to about 8, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition has a pD of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6.0 to about 7.0.

In some embodiments, useful formulations include one or more pD adjusting agents or buffering agents. Suitable pD adjusting agents or buffers include, but are not limited to acetate, bicarbonate, ammonium chloride, citrate, phosphate, deuterated forms of acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agents or buffers include deuterated hydrochloric acid (DCl), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).

In one embodiment, when one or more buffers are utilized in the formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and are present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%. In certain embodiments of the present disclosure, the amount of buffer included in the gel formulations are an amount such that the pD of the gel formulation does not interfere with the body's natural buffering system.

In one embodiment, diluents are also used to stabilize compounds because they provide a more stable environment. In some instances, salts dissolved in buffered solutions (which also provides pD control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

In some embodiments, the pD is calculated according to the formula disclosed in Glasoe et al., "Use of glass electrodes to measure acidities in deuterium oxide," J. Physical Chem. 64(1): 188-190 (1960). In some embodiment, the pD is calculated as $pD = pH^* + 0.4$, in which pH* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).

In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4 and about 8, between about 4.5 and about 8, between about 4.9 and about 7.9, between about 5.4 and about 7.9, between about 5.9 and about 7.9, between about 6.4 and about 7.9, or between about 7.4 and about 7.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.5, between about 5.0 and about 7.5, between about 5.5 and about 7.5, between about 6.0 and about 7.5, or between about 7.0 and about 7.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described

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In some instances, the ophthalmic aqueous composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.1. In some

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some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

In some embodiments, the pD of the ophthalmic aqueous composition described herein is associated with the stability of the ophthalmic aqueous composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a stable composition comprises a pD of less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments,

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ments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

In some embodiments, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., —OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., —OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the presence of deuterated water shifts the pK_a of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

In some embodiment, the ophthalmic gel or ointment composition described herein has a pD of about 4, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, or about 7.9.

In some embodiment, the pD of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization)) of ophthalmic formulations described herein. As used in the present disclosure, the term “aqueous composition” includes compositions that are based on D₂O.

In some embodiments, the pharmaceutical formulations described herein are stable with respect to pD over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9

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months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 18 months, at least about 24 months, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pD over a period of at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, or more.

Aqueous Solution Dose-To-Dose Uniformity

Typical ophthalmic aqueous solutions are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous solution includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous solution described herein is one drop of the aqueous solution composition from the eye drop bottle.

In some cases, described herein include ophthalmic aqueous compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake

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that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

Aqueous Solution Viscosity

In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10 to about 50,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 100 to about 40,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 500 to about 30,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 1000 to about 20,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 2000 to about 10,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 4000 to about 8000 cps at about 20° C. and sheer rate of 1 s⁻¹.

In some embodiments, the ophthalmic aqueous formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 50,000 centipoise, between about 750 and 50,000 centipoise; between about 1000 and 50,000 centipoise; between about 1000 and 40,000 centipoise; between about 2000 and 30,000 centipoise; between about 3000 and 20,000 centipoise; between about 4000 and 10,000 centipoise, or between about 5000 and 8000 centipoise.

In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an

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apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

Osmolarity

In some embodiments, a composition disclosed herein is formulated in order to not disrupt the ionic balance of the eye. In some embodiments, a composition disclosed herein has an ionic balance that is the same as or substantially the same as the eye. In some embodiments, a composition disclosed herein does not does not disrupt the ionic balance of the eye.

As used herein, “practical osmolarity/osmolality” or “deliverable osmolarity/osmolality” means the osmolarity/osmolality of a composition as determined by measuring the osmolarity/osmolality of the ophthalmic agent and all excipients except the gelling and/or the thickening agent (e.g., polyoxyethylene-polyoxypropylene copolymers, carboxymethylcellulose or the like). The practical osmolarity of a composition disclosed herein is measured by a suitable method, e.g., a freezing point depression method as described in Viegas et. al., *Int. J. Pharm.*, 1998, 160, 157-162. In some instances, the practical osmolarity of a composition disclosed herein is measured by vapor pressure osmometry (e.g., vapor pressure depression method) that allows for determination of the osmolarity of a composition at higher temperatures. In some instances, vapor pressure depression method allows for determination of the osmolarity of a composition comprising a gelling agent (e.g., a thermoreversible polymer) at a higher temperature wherein the gelling agent is in the form of a gel.

In some embodiments, the osmolarity at a target site of action (e.g., the eye) is about the same as the delivered osmolarity of a composition described herein. In some embodiments, a composition described herein has a deliverable osmolarity of about 150 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 280 mOsm/L to about 370 mOsm/L or about 250 mOsm/L to about 320 mOsm/L.

The practical osmolality of an ophthalmic composition disclosed herein is from about 100 mOsm/kg to about 1000 mOsm/kg, from about 200 mOsm/kg to about 800 mOsm/kg, from about 250 mOsm/kg to about 500 mOsm/kg, or from about 250 mOsm/kg to about 320 mOsm/kg, or from about 250 mOsm/kg to about 350 mOsm/kg or from about 280 mOsm/kg to about 320 mOsm/kg. In some embodiments, a composition described herein has a practical osmolality of about 100 mOsm/L to about 1000 mOsm/L, about 200 mOsm/L to about 800 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 250 mOsm/L to about 320 mOsm/L, or about 280 mOsm/L to about 320 mOsm/L.

In some embodiments, suitable tonicity adjusting agents include, but are not limited to any pharmaceutically acceptable sugar, salt or any combinations or mixtures thereof, such as, but not limited to dextrose, glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. In some instances, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

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In some embodiment, the ophthalmic compositions described herein include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Sterility

In some embodiments, the compositions are sterilized. Included within the embodiments disclosed herein are means and processes for sterilization of a pharmaceutical composition disclosed herein for use in humans. The goal is to provide a safe pharmaceutical product, relatively free of infection causing micro-organisms. The U. S. Food and Drug Administration has provided regulatory guidance in the publication "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing" available at: <http://www.fda.gov/cder/guidance/5882fnl.htm>, which is incorporated herein by reference in its entirety.

As used herein, sterilization means a process used to destroy or remove microorganisms that are present in a product or packaging. Any suitable method available for sterilization of objects and compositions is used. Available methods for the inactivation of microorganisms include, but are not limited to, the application of extreme heat, lethal chemicals, or gamma radiation. In some embodiments, a process for the preparation of an ophthalmic formulation comprises subjecting the formulation to a sterilization method selected from heat sterilization, chemical sterilization, radiation sterilization or filtration sterilization. The method used depends largely upon the nature of the device or composition to be sterilized. Detailed descriptions of many methods of sterilization are given in Chapter 40 of Remington: The Science and Practice of Pharmacy published by Lippincott, Williams & Wilkins, and is incorporated by reference with respect to this subject matter.

Filtration

Filtration sterilization is a method used to remove but not destroy microorganisms from solutions. Membrane filters are used to filter heat-sensitive solutions. Such filters are thin, strong, homogenous polymers of mixed cellulosic esters (MCE), polyvinylidene fluoride (PVF; also known as PVDF), or polytetrafluoroethylene (PTFE) and have pore sizes ranging from 0.1 to 0.22 μm . Solutions of various characteristics are optionally filtered using different filter membranes. For example, PVF and PTFE membranes are well suited to filtering organic solvents while aqueous solutions are filtered through PVF or MCE membranes. Filter apparatus are available for use on many scales ranging from the single point-of-use disposable filter attached to a syringe up to commercial scale filters for use in manufacturing plants. The membrane filters are sterilized by autoclave or chemical sterilization. Validation of membrane filtration systems is performed following standardized protocols (Microbiological Evaluation of Filters for Sterilizing Liquids, Vol 4, No. 3. Washington, D.C.: Health Industry Manufacturers Association, 1981) and involve challenging the membrane filter with a known quantity (ca. $10^7/\text{cm}^2$) of unusually small microorganisms, such as *Brevundimonas diminuta* (ATCC 19146).

Pharmaceutical compositions are optionally sterilized by passing through membrane filters. Formulations comprising nanoparticles (U.S. Pat. No. 6,139,870) or multilamellar vesicles (Richard et al., International Journal of Pharmaceu-

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tics (2006), 312(1-2):144-50) are amenable to sterilization by filtration through 0.22 μm filters without destroying their organized structure.

In some embodiments, the methods disclosed herein comprise sterilizing the formulation (or components thereof) by means of filtration sterilization. In ophthalmic gel compositions that includes thermosetting polymers, filtration is carried out below (e.g. about 5° C.) the gel temperature (Tgel) of a formulation described herein and with viscosity that allows for filtration in a reasonable time using a peristaltic pump (e.g. below a theoretical value of 100 cP).

Accordingly, provided herein are methods for sterilization of ophthalmic formulations that prevent degradation of polymeric components (e.g., thermosetting and/or other viscosity enhancing agents) and/or the ophthalmic agent during the process of sterilization. In some embodiments, degradation of the ophthalmic agent (e.g., a muscarinic antagonist such as atropine or atropine sulfate) is reduced or eliminated through the use of specific pH ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pH range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation Sterilization

One advantage of radiation sterilization is the ability to sterilize many types of products without heat degradation or other damage. The radiation commonly employed is beta radiation or alternatively, gamma radiation from a ^{60}Co source. The penetrating ability of gamma radiation allows its use in the sterilization of many product types, including solutions, compositions and heterogeneous mixtures. The germicidal effects of irradiation arise from the interaction of gamma radiation with biological macromolecules. This interaction generates charged species and free-radicals. Subsequent chemical reactions, such as rearrangements and cross-linking processes, result in the loss of normal function for these biological macromolecules. The formulations described herein are also optionally sterilized using beta irradiation.

Sterilization by Heat

Many methods are available for sterilization by the application of high heat. One method is through the use of a saturated steam autoclave. In this method, saturated steam at a temperature of at least 121° C. is allowed to contact the object to be sterilized. The transfer of heat is either directly to the microorganism, in the case of an object to be sterilized, or indirectly to the microorganism by heating the bulk of an aqueous solution to be sterilized. This method is widely practiced as it allows flexibility, safety and economy in the sterilization process.

Microorganisms

In some embodiments, the compositions are substantially free of microorganisms. Acceptable bioburden or sterility levels are based on applicable standards that define therapeutically acceptable compositions, including but not lim-

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ited to United States Pharmacopeia Chapters <111> et seq. For example, acceptable sterility (e.g., bioburden) levels include about 10 colony forming units (cfu) per gram of formulation, about 50 cfu per gram of formulation, about 100 cfu per gram of formulation, about 500 cfu per gram of formulation or about 1000 cfu per gram of formulation. In some embodiments, acceptable bioburden levels or sterility for formulations include less than 10 cfu/mL, less than 50 cfu/mL, less than 500 cfu/mL or less than 1000 cfu/mL microbial agents. In addition, acceptable bioburden levels or sterility include the exclusion of specified objectionable microbiological agents. By way of example, specified objectionable microbiological agents include but are not limited to *Escherichia coli* (*E. coli*), *Salmonella* sp., *Pseudomonas aeruginosa* (*P. aeruginosa*) and/or other specific microbial agents.

An important component of the sterility assurance quality control, quality assurance and validation process is the method of sterility testing. Sterility testing, by way of example only, is performed by two methods. The first is direct inoculation wherein a sample of the composition to be tested is added to growth medium and incubated for a period of time up to 21 days. Turbidity of the growth medium indicates contamination. Drawbacks to this method include the small sampling size of bulk materials which reduces sensitivity, and detection of microorganism growth based on a visual observation. An alternative method is membrane filtration sterility testing. In this method, a volume of product is passed through a small membrane filter paper. The filter paper is then placed into media to promote the growth of microorganisms. This method has the advantage of greater sensitivity as the entire bulk product is sampled. The commercially available Millipore Steritest sterility testing system is optionally used for determinations by membrane filtration sterility testing. For the filtration testing of creams or ointments Steritest filter system No. TLHVSL210 are used. For the filtration testing of emulsions or viscous products Steritest filter system No. TLAREM210 or TDA-REM210 are used. For the filtration testing of pre-filled syringes Steritest filter system No. TTHASY210 are used. For the filtration testing of material dispensed as an aerosol or foam Steritest filter system No. TTHVA210 are used. For the filtration testing of soluble powders in ampoules or vials Steritest filter system No. TTHADA210 or TTHADV210 are used.

Testing for *E. coli* and *Salmonella* includes the use of lactose broths incubated at 30-35° C. for 24-72 hours, incubation in MacConkey and/or EMB agars for 18-24 hours, and/or the use of Rappaport medium. Testing for the detection of *P. aeruginosa* includes the use of NAC agar. United States Pharmacopeia Chapter <62> further enumerates testing procedures for specified objectionable microorganisms.

In certain embodiments, the ophthalmic formulation described herein has less than about 60 colony forming units (CFU), less than about 50 colony forming units, less than about 40 colony forming units, or less than about 30 colony forming units of microbial agents per gram of formulation. In certain embodiments, the ophthalmic formulations described herein are formulated to be isotonic with the eye.

Endotoxins

An additional aspect of the sterilization process is the removal of by-products from the killing of microorganisms (hereinafter, "Product"). The process of depyrogenation removes pyrogens from the sample. Pyrogens are endotoxins or exotoxins which induce an immune response. An example of an endotoxin is the lipopolysaccharide (LPS)

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molecule found in the cell wall of gram-negative bacteria. While sterilization procedures such as autoclaving or treatment with ethylene oxide kill the bacteria, the LPS residue induces a proinflammatory immune response, such as septic shock. Because the molecular size of endotoxins varies widely, the presence of endotoxins is expressed in "endotoxin units" (EU). One EU is equivalent to 100 picograms of *E. coli* LPS. In some cases, humans develop a response to as little as 5 EU/kg of body weight. The bioburden (e.g., microbial limit) and/or sterility (e.g., endotoxin level) is expressed in any units as recognized in the art. In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g., <4 EU/kg of body weight of a subject) when compared to conventionally acceptable endotoxin levels (e.g., 5 EU/kg of body weight of a subject). In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of body weight of a subject. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 2 EU/kg of body weight of a subject.

In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of formulation. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of formulation. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of formulation. In some embodiments, the ophthalmic formulation has less than about 5 EU/kg Product. In other embodiments, the ophthalmic formulation has less than about 1 EU/kg Product. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/kg Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/g of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/g of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/g of unit or Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/mg of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/mg of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/mg of unit or Product. In certain embodiments, ophthalmic formulations described herein contain from about 1 to about 5 EU/mL of formulation. In certain embodiments, ophthalmic formulations described herein contain from about 2 to about 5 EU/mL of formulation, from about 3 to about 5 EU/mL of formulation, or from about 4 to about 5 EU/mL of formulation.

In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g., <0.5 EU/mL of formulation) when compared to conventionally acceptable endotoxin levels (e.g., 0.5 EU/mL of formulation). In some embodiments, the ophthalmic formulation has less than about 0.5 EU/mL of formulation. In other embodiments, the ophthalmic formulation has less than about 0.4 EU/mL of formulation. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/mL of formulation.

Pyrogen detection, by way of example only, is performed by several methods. Suitable tests for sterility include tests described in United States Pharmacopoeia (USP) <71> Sterility Tests (23rd edition, 1995). The rabbit pyrogen test and the Limulus amoebocyte lysate test are both specified in the United States Pharmacopeia Chapters <85> and <151> (USP23/NF 18, Biological Tests, The United States Pharmacopoeial Convention, Rockville, Md., 1995). Alternative

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pyrogen assays have been developed based upon the monocyte activation-cytokine assay. Uniform cell lines suitable for quality control applications have been developed and have demonstrated the ability to detect pyrogenicity in samples that have passed the rabbit pyrogen test and the Limulus amoebocyte lysate test (Taktak et al, J. Pharm. Pharmacol. (1990), 43:578-82). In an additional embodiment, the ophthalmic formulation is subject to depyrogenation. In a further embodiment, the process for the manufacture of the ophthalmic formulation comprises testing the formulation for pyrogenicity. In certain embodiments, the formulations described herein are substantially free of pyrogens.

Ophthalmic Muscarinic Antagonist-Mucus Penetrating Particle (MPP) Composition

Mucus-penetrating particles (MPPs) are particles that rapidly traverse mucus (e.g. human mucus). In some cases, MPPs comprise of a nanoparticle with a particle size of between about 200 nm and 500 nm. In some instances, the nanoparticle is further coated with a mucus penetrating agent. In some instances, a composition described herein is formulated with MPPs for mucus penetration. In some instances, an ophthalmic agent composition described herein is formulated with MPPs for mucus penetration. In some instances, the ophthalmic agent is a muscarinic antagonist. In some instances, a muscarinic antagonist composition described herein is formulated with MPPs for mucus penetration. In some instances, a muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolamine (L-hyoscyne), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine. In some instances, a muscarinic antagonist is atropine or its pharmaceutically acceptable salt thereof. In some instances, a muscarinic antagonist is atropine sulfate. In some instances, an atropine composition described herein is formulated with MPPs for mucus penetration. In some instances, an atropine sulfate composition described herein is formulated with MPPs for mucus penetration. In a non-limiting example, the MPPs for use in the disclosed composition is obtained from Kala Pharmaceuticals, Inc. (100 Beaver Street #201, Waltham, Mass. 02453).

In some embodiments, the nanoparticle comprises of any suitable material, such as an organic material, an inorganic material, a polymer, or combinations thereof. In some instances, the nanoparticle comprises of inorganic material, such as for example, a metal (e.g., Ag, Au, Pt, Fe, Cr, Co, Ni, Cu, Zn, and other transition metals), a semiconductor (e.g., silicon, silicon compounds and alloys, cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide), or an insulator (e.g., ceramics such as silicon oxide). In some instances, the nanoparticle comprises organic materials such as a synthetic polymer and/or a natural polymer. Examples of synthetic polymers include non-degradable polymers such as polymethacrylate and degradable polymers such as polylactic acid, polyglycolic acid and copolymers thereof. Examples of natural polymers include hyaluronic acid, chitosan, and collagen.

In some embodiments, the nanoparticle is coated with a mucus penetrating agent. In some instances, the mucus penetrating agent comprises any suitable material, such as a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some instances, the mucus penetrat-

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ing agent is a polymer. In some instances, the polymer a synthetic polymer (i.e., a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (e.g., a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer is a diblock copolymer, a triblock copolymer, e.g., e.g., where one block is a hydrophobic polymer and another block is a hydrophilic polymer. In some embodiments, the polymer is charged or uncharged.

Additional examples of suitable polymers include, but are not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, poly sulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, poly isocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.

In some cases, an ophthalmic agent (e.g. a muscarinic antagonist such as atropine or atropine sulfate) is present in the MPP formulation at a concentration of between about 0.001 wt % and about 0.05 wt %, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable pro-drug or salt thereof, by weight of the composition. In some

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instances, additional agents such as buffers, pH adjusting agents, and/or preservatives are formulated in the MPP formulation.

In some instances, ophthalmic agent-MPP composition is formulated using any suitable method. In some embodiments, a milling process is used to reduce the size of a solid material to form particles in the micrometer to nanometer size range. In some cases, dry and wet milling processes such as jet milling, cryo-milling, ball milling, media milling, and homogenization are known and are used in methods described herein. Generally, in a wet milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. Dry milling is a process wherein the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. In a cryo-milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients under cooled temperatures.

In some embodiments, any suitable grinding medium is used for milling. In some embodiments, a ceramic and/or polymeric material and/or a metal is used. Examples of suitable materials include zirconium oxide, silicon carbide, silicon oxide, silicon nitride, zirconium silicate, yttrium oxide, glass, alumina, alpha-alumina, aluminum oxide, polystyrene, poly(methyl methacrylate), titanium, steel. In some cases, a grinding medium has any suitable size. For example, the grinding medium has an average diameter of at least about 0.1 mm, at least about 0.2 mm, at least about 0.5 mm, at least about 0.8 mm, at least about 1 mm, at least about 2 mm, or at least about 5 mm. In some cases, the grinding medium has an average diameter of less than or equal to about 5 mm, less than or equal to about 2 mm, less than or equal to about 1 mm, less than or equal to about 0.8 mm, less than or equal to about 0.5 mm, or less than or equal to about 0.2 mm. Combinations of the above-referenced ranges are also possible (e.g., an average diameter of at least about 0.5 millimeters and less than or equal to about 1 mm). Other ranges are also possible.

In some embodiments, any suitable solvent are used for milling. In some cases, the choice of solvent is depend on factors such as the solid material (e.g., a muscarinic antagonist such as atropine) being milled, the particular type of stabilizer/mucus penetrating agent being used (e.g., one that renders the particle mucus penetrating), the grinding material to be used, among other factors. In some cases, suitable solvents are ones that do not substantially dissolve the solid material or the grinding material, but dissolve the stabilizer/mucus penetrating agent to a suitable degree. Non-limiting examples of solvents include, but are not limited to, water, buffered solutions, other aqueous solutions, alcohols (e.g., ethanol, methanol, butanol), and mixtures thereof that optionally include other components such as pharmaceutical excipients, polymers, pharmaceutical agents, salts, preservative agents, viscosity modifiers, tonicity modifier, taste masking agents, antioxidants, pH modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent is used. In some cases, a pharmaceutical agent (e.g. a muscarinic antagonist such as atropine) has any suitable solubility in these or other solvents, such as a solubility in one or more of the ranges described above for aqueous solubility or for solubility in a coating solution.

In some instances, a MPP is a MPP as described in WO2013/166385. In some instances, a MPP is a MPP as described in Lai et al., "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," *PNAS* 104 (5):1482-1487 (2007). In some instances, an ophthalmic

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agent-MPP composition is formulated using a method as described in WO2013/166385. In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in Lai et al., "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," *PNAS* 104(5):1482-1487 (2007). In some instances, the ophthalmic agent is a muscarinic antagonist such as atropine or atropine sulfate.

Muscarinic Antagonist-Ophthalmic Delivery Devices and Delivery System

In some embodiments, a muscarinic antagonist described herein is delivered to a target site by an ophthalmic delivery device. In some cases, the ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist comprises atropine or atropine sulfate.

In some embodiments, an ophthalmic delivery device comprises a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device. In some instances, a non-invasive delivery device comprises topical ophthalmic drug delivery device (TODD) or a contact lens. In some instances, the ophthalmic delivery device is a biodegradable ophthalmic delivery device. In other instances, the ophthalmic delivery device is a non-biodegradable ophthalmic delivery device. In some cases, the biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In other cases, the non-biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist.

In some instances, an ophthalmic delivery device comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In some cases, the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the ophthalmic delivery device, and is configured for a controlled sustained release of the muscarinic antagonist. In some instances, the ophthalmic delivery device is a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device.

Punctal Plug

A punctal plug or tear duct plug is an ocular device that in some cases is inserted into the tear duct (or puncta) of an eye. In some instances, a punctal plug is used for the delivery of an ophthalmic composition, for example, an ophthalmic composition described herein. In some cases, a punctal plug is used for the delivery of a muscarinic antagonist formulated in deuterated water. In additional cases, a punctal plug is used for the delivery of atropine or atropine sulfate formulated in deuterated water.

In some instances, a punctal plug is used for controlled sustained release of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the period of controlled sustained release is, for example, up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 30, 45, 60 days or longer. In some instances, the period of controlled sustained release is, for example, up to 7 days. In some cases, the period of con-

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trolled sustained release is, for example, up to 14 days. In some cases, the period of controlled sustained release is, for example, up to 1 month.

In some embodiments, a punctal plug comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed within the punctal plug material, and is configured for a controlled sustained release of the muscarinic antagonist.

In some embodiments, a punctal plug described herein utilizes a diffusion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some instances, the configuration of the punctal plug is tubular with its cylindrical wall closed by transverse end walls to define a reservoir for the muscarinic antagonist (either in liquid or gel form), in some cases, at least the cylindrical wall is a membrane permeable by diffusion so that the muscarinic antagonist is released continuously at a controlled rate through the membrane into the tear fluid.

Exemplary materials for a permeable membrane for the diffusion mechanism include insoluble microporous materials of polycarbonates, polyvinyl chlorides, polyamides, copolymers of polyvinyl chloride and acrylonitrile, polysulfones, polyvinylidene fluorides, polyvinyl fluorides, polychloroethers, polyformaldehydes, acrylic resins, polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetates, polyethers, cellulose esters, porous rubbers, cross-linked poly(ethylene oxide), cross-linked polyvinyl pyrrolidone, cross-linked poly(vinyl alcohol) and polystyrenes.

In some embodiments, a punctal plug described herein utilizes an osmosis mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is tubular with domed end walls, and the device comprises a transverse impermeable elastic membrane dividing the tubular interior of the device into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. In some cases, a drug release aperture is included in the impermeable end wall of the device. When the device is placed in the aqueous environment of the eye water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

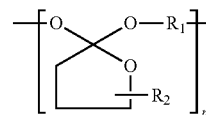
Examples of materials for an osmotic semi-permeable membrane include cellulose acetate and its derivatives, partial and completely hydrolyzed ethylene-vinyl acetate copolymers, highly plasticized polyvinyl chloride, homo- and copolymers of polyvinyl acetate, polyesters of acrylic acid and methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride; silicone polycarbonates, aromatic nitrogen-containing polymeric membranes, polymeric epoxides, copolymers of an alkylene oxide and alkyl glycidyl ether, polyurethanes, polyglycolic or polylactic acid and derivatives thereof, derivatives of polystyrene such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), ethylene-vinyl acetate copolymers.

In some embodiments, a punctal plug described herein utilizes a bioerosion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is rod-like being constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the device with tear

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fluid results in controlled sustained release of the drug by bioerosion of the matrix. In such cases, the drug is dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

Examples of bioerodible matrix materials include polyesters of the general formula —O—(W)—CO— and mixture thereof, wherein W is a lower alkylene of 1 to 7 carbons and may include a member selected from the group of alkylenes of the formula $\text{—CH}_2\text{—}$ or $\text{—CH—CH}_2\text{—}$, and Y has a value such that the molecular weight of the polymer is from about 4,000 to 100,000. The polymers are polymerization-condensation products of monobasic hydroxy acid of the formula $\text{C}_n\text{H}_{2n}(\text{OH})\text{COOH}$ wherein n has a value of 1 to 7, preferably 1 or 2 and the acid is especially lactic acid or glycolic acid. Also included are copolymers derived from mixtures of these acids. Bioerodible materials also include poly(orthoesters). These materials have the following general formula:



wherein R_1 is an alkylene of 4 to 12 carbons, a cycloalkylene of 5 to 6 carbons substituted with an alkylene of 1 to 7 carbons and an alkyleneoxy of 1 to 7 carbons, and R_2 is a lower alkyl of 1 to 7 carbons.

Additional bioerodible matrix materials include: (1) Poly-anhydrides such as poly(p-carboxyphenoxy) alkyl (e.g. p-carboxyphenoxypropane) or polymeric fatty acid diester (e.g. poly-dodecanedioic acid) compounds and further copolymers with sebacic acid, or phthalic acid such as disclosed in Chasin et al., Poly-anhydrides for Controlled Drug Delivery, *Biopharm.*, February 1988, 33-46; and Lee et al, (1988), The Use of Bioerodible Polymers and 5 fluorouracil in Glaucoma Filtration Surgery, invest. *Ophthalmol. Vis. Sci.*, 29, 1692-1697; (2) Poly (alkyl-2-cyanoacrylates) such as poly (hexyl-2-cyanoacrylate) as described by Douglas et al. (1987), Nanoparticles in Drug Delivery, CRC Crit. Rev. Therap. Drug Carr. System., 3, 233-261; and (3) Polyamino acids such as copolymers of leucine and methyl glutamate.

In some cases, a punctal plug described herein comprises a solid non-erodible rod with pores. In some instances, the release of a muscarinic antagonist takes place via diffusion through the pores. In such instances, controlled release is further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

Examples of materials for use as non-erodible rods include polymers such as hydroxyethylmethacrylate and co-polymers with methacrylic acid, methylmethacrylate, N-vinyl 2-pyrrolidone, allyl methacrylate, ethylene glycol dimethacrylate, ethylene dimethacrylate, or 1,1,1 trimethylolpropane trimethacrylate, and dimethyl diphenyl methyl-vinyl polysiloxane.

In some instances, the body of the plug is wholly or partially transparent or opaque. Optionally, the body includes a tint or pigment that makes the plug easier to see when it is placed in a punctum.

In some cases, the surface of the plug body is wholly or partially coated. In some cases, the coating provides one or more of lubriciousness to aid insertion, muco-adhesiveness to improve tissue compatibility, and texture to aid in anchor-

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ing the plug within the punctum. Examples of suitable coatings include, without limitation, gelatin, collagen, hydroxyethyl methacrylate, PVP, PEG, heparin, chondroitin sulphate, hyaluronic acid, synthetic and natural proteins, and polysaccharides, thiomers, thiolated derivatives of polyacrylic acid and chitosan, polyacrylic acid, carboxymethyl cellulose and the like and combinations thereof.

In some embodiments, a punctal plug described herein is a punctal plug described in U.S. Pat. No. 5,147,647; U.S. Publication No. 2012/0277694; or 2010/0256557.

In some instances, the size of the opening of the punctal plug is from about 0.05 mm to about 2.5 mm. In some instances, it is from about 0.1 mm to about 2.0 mm, or from about 0.15 mm to about 1 mm.

In some embodiments, the amount of a muscarinic antagonist (e.g., atropine or atropine sulfate) used in the plugs depends upon the muscarinic antagonist selected, the desired doses to be delivered via the punctal plug, the desired release rate, and the melting points of the muscarinic antagonist and muscarinic antagonist-containing material.

Scleral Patch or Scleral Ring

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a scleral patch or a scleral ring. In some instances, a scleral patch or a scleral ring is a biodegradable scleral patch or scleral ring. In other instances, a scleral patch or a scleral ring is a non-biodegradable scleral patch or scleral ring. In additional instances, a scleral patch or a scleral ring is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a scleral patch comprises a multi-layered patch in which one or more layer within the patch comprises a muscarinic antagonist described herein. In some cases, a scleral ring comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the scleral patch or the scleral ring.

Cul-De Sac Inserts

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a Cul-de sac insert. In some instances, the Cul-de sac insert comprises a single-layered device comprising muscarinic antagonist dispersed within the insert material, or multilayered, solid or semisolid consistency insert. In some instances, the Cul-de sac insert is a biodegradable insert. In other instances, the Cul-de sac insert is a non-biodegradable insert. In additional instances, a Cul-de sac insert is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some instances, a Cul-de sac insert comprises a membrane-bound ocular insert, which comprises of two outer layers of a copolymer such as ethylene-vinyl acetate copolymer (EVA) and an inner layer comprising a muscarinic antagonist. In some instances, the muscarinic antagonist within the inner layer is formulated as a gel or as a solution. An exemplary membrane-bound ocular insert is Ocuserts from Alza Corp.

In some cases, a Cul-de sac insert comprises an ocular film or sheath (mucoadhesive film or sheath or collagen shields), a coil, a polymer rod, HEMA hydrogel, or polysulfone capillary fiber. In some instances, a Cul-de sac insert comprises rod-shaped water soluble insert comprising of hydroxypropyl cellulose, a muscarinic antagonist, and one or more additional excipients. In some instances, the Cul-de

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sac insert comprising a rod-shaped water soluble insert is a biodegradable insert. An example comprises Lacrisert (Merck).

Subconjunctival/Episcleral Implant

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a subconjunctival/episcleral implant. In some instances, a subconjunctival/episcleral implant is a biodegradable implant. In other instances, a subconjunctival/episcleral implant is a non-biodegradable implant. In additional instances, a subconjunctival/episcleral implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a subconjunctival/episcleral implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the subconjunctival/episcleral implant. Exemplary subconjunctival/episcleral implants include LX201 (Lux Biosciences Inc.), an episcleral implant from 3T Ophthalmics, or a subconjunctival insert from Pfizer.

Intravitreal Implants

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through an intravitreal implant. In some instances, an intravitreal implant is a biodegradable implant. In other instances, an intravitreal implant is a non-biodegradable implant. In additional instances, an intravitreal implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, an intravitreal implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the intravitreal implant. Exemplary intravitreal implant comprises Durasert™ technology system (pSivida Corp.) (such as Vitrasert® and Retisert® from Bausch & Lomb Inc, and Iluvien® from Alimera sciences), Novadur™ technology system (such as Ozurdex® from Allergan), I-Vation™ technology system (such as a delivery system developed from SurModics, Inc.), and NT-501 from Neurotech Pharmaceuticals.

Non-Invasive Delivery System

In some embodiments, a non-invasive delivery system comprises a topical ophthalmic agent delivery device. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device comprises a soft elastomer drug depot that floats atop the sclera under the eyelid. In some instances, the topical ophthalmic agent delivery device is a biodegradable delivery device. In other instances, the topical ophthalmic agent delivery device is a non-biodegradable delivery device. In some cases, the topical ophthalmic agent delivery device is impregnated with a muscarinic antagonist described herein. In other cases, a muscarinic antagonist is dispersed (e.g., uniformly) in the topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device is formulated for controlled sustained release of the muscarinic antagonist. In some instances, an exemplary delivery device is a topical ophthalmic drug delivery device (TODD) from Amorphex Therapeutics.

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In some embodiments, a non-invasive delivery system comprises a contact lens. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a contact lens. In some instances, the contact lens is impregnated with a muscarinic antagonist, for example, in which the muscarinic antagonist is dispersed, e.g., as colloidal structure, within the lens. In other instances, the contact lens is further combined with a muscarinic antagonist layer, and is configured for controlled sustained release to the eye. Exemplary polymers, e.g., hydrogel copolymers, for making a contact lens include at least one hydrophilic monomer and a crosslinking agent (a crosslinker being defined as a monomer having multiple polymerizable functionalities). Representative, hydrophilic monomers include: unsaturated carboxylic acids, such as methacrylic acid and acrylic acid; (meth)acrylic substituted alcohols, such as 2-hydroxyethylmethacrylate and 2-hydroxyethylacrylate; vinyl lactams, such as N-vinyl pyrrolidone; and (meth) acrylamides, such as methacrylamide and N,N-dimethylacrylamide. Typical crosslinking agents include polyvinyl, typically di- or tri-vinyl monomers, such as di- or tri(meth) acrylates of diethyleneglycol, triethyleneglycol, butyleneglycol and hexane-1,6-diol; and divinylbenzene. A specific example of a hydrogel-forming monomer mixture is polymacon, composed primarily of 2-hydroxyethylmethacrylate with a small amount of diethyleneglycol dimethacrylate as a crosslinking monomer. Optionally, the monomer mixture may include a silicone-containing monomer in order to form a silicone hydrogel copolymer. Examples of silicone-containing monomers include: monomers including a single activated unsaturated radical, such as methacryloxypropyl tris(trimethylsiloxy)silane, pentamethyldisiloxanyl methylmethacrylate, tris(trimethylsiloxy)methacryloxypropylsilane, methyl di(trimethylsiloxy)methacryloxymethylsilane, 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbamate, and 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbonate; and multifunctional ethylenically "end-capped" siloxane-containing monomers, especially difunctional monomers having two activated unsaturated radicals. A specific example of a silicone hydrogel-forming monomer mixture is balafilcon, based on N-vinyl pyrrolidone and the aforementioned vinyl carbonate and carbamate monomers, disclosed in U.S. Pat. No. 5,260,000.

Ophthalmic Gel Muscarinic Antagonist Composition

Gels have been defined in various ways. For example, the United States Pharmacopoeia defines gels as semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels include a single-phase or a two-phase system. A single-phase gel consists of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Some single-phase gels are prepared from synthetic macromolecules (e.g., carbomer) or from natural gums, (e.g., tragacanth). In some embodiments, single-phase gels are generally aqueous, but will also be made using alcohols and oils. Two-phase gels consist of a network of small discrete particles.

In some embodiments, gels are also classified as being hydrophobic or hydrophilic. In certain embodiments, the base of a non-limiting example of a hydrophobic gel includes a liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, or aluminum or zinc soaps. In contrast, the base of a non-limiting example of a hydrophilic gel includes water, glycerol, or propylene glycol gelled with a suitable gelling agent (e.g., tragacanth, starch, cellulose derivatives, carboxyvinyl polymers, and magnesium-alumi-

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num silicates). In certain embodiments, the rheology of the compositions disclosed herein is pseudo plastic, plastic, thixotropic, or dilatant.

In some embodiments, the ophthalmic composition is an ophthalmic gel, and wherein the ophthalmically acceptable carrier comprises water and at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

In some embodiment, the ophthalmic gel composition described herein is a semi-solid or id in a gelled state before it is topically administered (e.g. at room temperature). For example, suitable viscosity-enhancing agents for such gels include by way of example only, gelling agents and suspending agents. In one embodiment, the enhanced viscosity formulation does not include a buffer. In other embodiments, the enhanced viscosity formulation includes a pharmaceutically acceptable buffer. Sodium chloride or other tonicity agents are optionally used to adjust tonicity, if necessary.

By way of example only, the ophthalmically acceptable viscosity agent includes hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate. Other viscosity enhancing agents compatible with the targeted ocular site include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chitin, carboxymethylated chitosan, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthum gum, gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, poly geline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), Splenda® (dextrose, maltodextrin and sucralose) or combinations thereof. In specific embodiments, the viscosity-enhancing excipient is a combination of MCC and CMC. In another embodiment, the viscosity-enhancing agent is a combination of carboxymethylated chitosan, or chitin, and alginate. The combination of chitin and alginate with the ophthalmic agents disclosed herein acts as a controlled release formulation, restricting the diffusion of the ophthalmic agents from the formulation. Moreover, the combination of carboxymethylated chitosan and alginate is optionally used to assist in increasing the permeability of the ophthalmic agents in the eye.

In some embodiments is an enhanced viscosity formulation, comprising from about 0.1 mM and about 100 mM of an ophthalmic agent, a pharmaceutically acceptable viscosity agent, and water for injection, the concentration of the viscosity agent in the water being sufficient to provide an enhanced viscosity formulation with a final viscosity from about 100 to about 100,000 cP. In certain embodiments, the viscosity of the gel is in the range from about 100 to about

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50,000 cP, about 100 cP to about 1,000 cP, about 500 cP to about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 50,000 cP, about 10,000 cP to about 500,000 cP, about 15,000 cP to about 1,000,000 cP. In other embodiments, when an even more viscous medium is desired, the biocompatible gel comprises at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 70%, at least about 75%, or even at least about 80% or so by weight of the ophthalmic agent. In highly concentrated samples, the biocompatible enhanced viscosity formulation comprises at least about 25%, at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 75%, at least about 85%, at least about 90% or at least about 95% or more by weight of the ophthalmic agent.

In one embodiment, the pharmaceutically acceptable enhanced viscosity ophthalmically acceptable formulation comprises at least one ophthalmic agent and at least one gelling agent. Suitable gelling agents for use in preparation of the gel formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum and any combinations or mixtures thereof. In some other embodiments, hydroxypropylmethylcellulose (Methocel®) is utilized as the gelling agent. In certain embodiments, the viscosity enhancing agents described herein are also utilized as the gelling agent for the gel formulations presented herein.

In some embodiments, the ophthalmic gel composition described herein is an in situ gel formulation. In some instances, the in situ gel formation is based on increased pre-corneal residence time of the ophthalmic composition which improves ocular bioavailability, corneal mucoadhesion, lysosomal interaction and ionic gelation, improved corneal absorption, thermal gelation, or a combination thereof. In some instances, the in situ gel formulation is activated by pH, temperature, ion, UV, or solvent exchange.

In some instances, the ophthalmic gel composition comprises a muscarinic antagonist and one or more gelling agents. In some instances, the gelling agent includes, but is not limited to, poloxamer (e.g. Poloxamer 407), tetratics, ethyl (hydroxyethyl) cellulose, cellulose acetate phthalate (CAP), carbopol (e.g. Carbopol 1342P NF, Carbopol 980 NF), alginates (e.g. low acetyl gellan gum (Gelrite®)), gellan, hyaluronic acid, pluronics (e.g. Pluronic F-127), chitosan, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), dextran, hydroxy propyl methyl cellulose (HPMC), hydroxyethylcellulose (HEC), methylcellulose (MC), thiolated xyloglucan, polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, xyloglucans, or combinations thereof.

In some instances, the in situ gel formation further comprises a permeation enhancer. In some instances, the permeation enhancer includes surfactants (e.g. non-ionic surfactants), benzalkonium chloride, EDTA, surface-active heteroglycosides, calcium chelators, hydroxyl propyl beta cyclodextrin (HP beta CD), bile salts, and the like.

In some embodiments, other gel formulations are useful depending upon the particular ophthalmic agent, other pharmaceutical agent or excipients/additives used, and as such are considered to fall within the scope of the present disclosure. For example, other commercially-available glycerin-based gels, glycerin-derived compounds, conjugated, or

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crosslinked gels, matrices, hydrogels, and polymers, as well as gelatins and their derivatives, alginates, and alginate-based gels, and even various native and synthetic hydrogel and hydrogel-derived compounds are all expected to be useful in the ophthalmic agent formulations described herein. In some embodiments, ophthalmically acceptable gels include, but are not limited to, alginate hydrogels SAF®-Gel (ConvaTec, Princeton, N.J.), Duoderm® Hydroactive Gel (ConvaTec), Nu-gel® (Johnson & Johnson Medical, Arlington, Tex.); Carrasyn® (V) Acemannan Hydrogel (Carrington Laboratories, Inc., Irving, Tex.); glycerin gels Elta® Hydrogel (Swiss-American Products, Inc., Dallas, Tex.) and K-Y® Sterile (Johnson & Johnson). In further embodiments, biodegradable biocompatible gels also represent compounds present in ophthalmically acceptable formulations disclosed and described herein.

In some embodiments, the viscosity-enhancing agent is a cellulose-based polymer selected from cellulose gum, alkylcellulose, hydroxyl-alkyl cellulose, hydroxyl-alkyl alkylcellulose, carboxy-alkyl cellulose, or combinations thereof. In some embodiments, the viscosity-enhancing agent is hydroxyl-alkyl alkylcellulose. In some embodiment, the viscosity-enhancing agent is hydroxypropyl methylcellulose.

In certain embodiments, the enhanced viscosity formulation is characterized by a phase transition between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42° C.). In some embodiments, the phase transition occurs at 1° C. below body temperature, at 2° C. below body temperature, at 3° C. below body temperature, at 4° C. below body temperature, at 6° C. below body temperature, at 8° C. below body temperature, or at 10° C. below body temperature. In some embodiments, the phase transition occurs at about 15° C. below body temperature, at about 20° C. below body temperature or at about 25° C. below body temperature. In specific embodiments, the gelation temperature (Tgel) of a formulation described herein is about 20° C., about 25° C., or about 30° C. In certain embodiments, the gelation temperature (Tgel) of a formulation described herein is about 35° C., or about 40° C. Included within the definition of body temperature is the body temperature of a healthy individual, or an unhealthy individual, including an individual with a fever (up to -42° C.). In some embodiments, the pharmaceutical compositions described herein are liquids at about room temperature and are administered at or about room temperature.

Copolymers polyoxypropylene and polyoxyethylene (e.g. polyoxyethylene-polyoxypropylene triblock copolymers) form thermosetting gels when incorporated into aqueous solutions. These polymers have the ability to change from the liquid state to the gel state at temperatures close to body temperature, therefore allowing useful formulations that are applied to the targeted ocular site. The liquid state-to-gel state phase transition is dependent on the polymer concentration and the ingredients in the solution.

In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 15%, about 20%, about 25%, about 30%, about 35% or about 40% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24% or about 25% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in

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any formulation described herein is about 7.5% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 10% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 11% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 12% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 13% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 14% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 15% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 16% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 17% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 18% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 19% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 20% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 21% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 23% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 25% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 1%, about 5%, about 10%, or about 15% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, or about 5% of the total weight of the formulation.

In an alternative embodiment, the thermogel is a PEG-PLGA-PEG triblock copolymer (Jeong et al, *Nature* (1997), 388:860-2; Jeong et al, *J. Control. Release* (2000), 63:155-63; Jeong et al, *Adv. Drug Delivery Rev.* (2002), 54:37-51). The polymer exhibits sol-gel behavior over a concentration of about 5% w/w to about 40% w/w. Depending on the properties desired, the lactide/glycolide molar ratio in the PLGA copolymer ranges from about 1:1 to about 20:1. The resulting copolymers are soluble in water and form a free-flowing liquid at room temperature, but form a hydrogel at body temperature. A commercially available PEG-PLGA-PEG triblock copolymer is RESOMER RGP t50106 manufactured by Boehringer Ingelheim. This material is com-

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posed of a PLGA copolymer of 50:50 poly(DL-lactide-co-glycolide) and is 10% w/w of PEG and has a molecular weight of about 6000.

Additional biodegradable thermoplastic polyesters include AtriGel® (provided by Atrix Laboratories, Inc.) and/or those disclosed, e.g., in U.S. Pat. Nos. 5,324,519; 4,938,763; 5,702,716; 5,744,153; and 5,990,194; wherein the suitable biodegradable thermoplastic polyester is disclosed as a thermoplastic polymer. Examples of suitable biodegradable thermoplastic polyesters include polylactides, polyglycolides, polycaprolactones, copolymers thereof, terpolymers thereof, and any combinations thereof. In some such embodiments, the suitable biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof. In one embodiment, the biodegradable thermoplastic polyester is 50/50 poly(DL-lactide-co-glycolide) having a carboxy terminal group; is present in about 30 wt. % to about 40 wt. % of the composition; and has an average molecular weight of about 23,000 to about 45,000. Alternatively, in another embodiment, the biodegradable thermoplastic polyester is 75/25 poly (DL-lactide-co-glycolide) without a carboxy terminal group; is present in about 40 wt. % to about 50 wt. % of the composition; and has an average molecular weight of about 15,000 to about 24,000. In further or alternative embodiments, the terminal groups of the poly(DL-lactide-co-glycolide) are either hydroxyl, carboxyl, or ester depending upon the method of polymerization. Polycondensation of lactic or glycolic acid provides a polymer with terminal hydroxyl and carboxyl groups. Ring-opening polymerization of the cyclic lactide or glycolide monomers with water, lactic acid, or glycolic acid provides polymers with the same terminal groups. However, ring-opening of the cyclic monomers with a monofunctional alcohol such as methanol, ethanol, or 1-dodecanol provides a polymer with one hydroxyl group and one ester terminal groups. Ring-opening polymerization of the cyclic monomers with a diol such as 1,6-hexanediol or polyethylene glycol provides a polymer with only hydroxyl terminal groups.

Since the polymer systems of thermosetting gels dissolve more completely at reduced temperatures, methods of solubilization include adding the required amount of polymer to the amount of water to be used at reduced temperatures. Generally after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostatic container at about 0-10° C. in order to dissolve the polymer. The mixture is stirred or shaken to bring about a more rapid dissolution of the thermosetting gel polymer. The ophthalmic agent and various additives such as buffers, salts, and preservatives are subsequently added and dissolved. In some instances the pharmaceutically agent is suspended if it is insoluble in water. The pH is modulated by the addition of appropriate buffering agents.

Ophthalmic Ointment Muscarinic Antagonist Composition

An ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (e.g. oil 80%-water 20%) with a high viscosity, intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that it contains. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an eye ointment), vulva, anus, and nose

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The vehicle of an ointment is known as the ointment base. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are: hydrocarbon bases, e.g. hard paraffin, soft paraffin, microcrystalline wax and ceresine; absorption bases, e.g. wool fat, beeswax; water soluble bases, e.g. macrogols 200, 300, 400; emulsifying bases, e.g. emulsifying wax, cetrimide; vegetable oils, e.g. olive oil, coconut oil, sesame oil, almond oil and peanut oil.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. In some embodiments, they are also derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases. The active agents are dispersed in the base, and later they get divided after the drug penetration into the target sites (e.g. membranes, skins, etc.).

The present disclosure recognizes that it is sometimes difficult to incorporate into the ointment a drug of low concentration with sufficient dose-to-dose uniformity for effectively treating a disorder or disease. In some embodiments, poly(ethylene-glycols), polyethoxylated castor oils (Cremophor® EL), alcohols having 12 to 20 carbon atoms or a mixture of two or more of said components are effective excipients for dispersing and/or dissolving effective amounts of ophthalmic drugs, in particular of ascomycins and staurosporine derivatives, in an ointment base, in particular in an ointment base substantially comprising oleaginous and hydrocarbon components, and that the resulting ointments are excellently tolerated by the skin and by ocular tissue.

The present disclosure further recognizes that ophthalmic drugs, such as a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), incorporated in the ointment compositions describes herein target the choroid and/or retina in a patient when the compositions are topically administered to the ocular surface, in particular to the sclera of said patient. In some embodiments, an ophthalmic ointment composition includes an ophthalmic drug, an ointment base and an agent for dispersing and/or dissolving said drug in the ointment base, selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components.

In some embodiments, the ointment bases include ophthalmically acceptable oil and fat bases, such as natural wax e.g. white and yellow bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax e.g. hard paraffin, microcrystalline wax; hydrocarbons e.g. liquid paraffin, white and yellow soft paraffin, white petrolatum, yellow petrolatum; or combinations thereof.

The above mentioned oil and fat bases are described in more detail, for instance, in the British Pharmacopoeia, Edition 2001, or the European Pharmacopoeia, 3rd Edition.

In some embodiments, the ointment base is present in amounts of about 50 to about 95, preferably of 70 to 90% by weight based on the total weight of the composition.

A preferred ointment base comprises a combination of one or more of one or more natural waxes like those indicated above, preferably wool wax (wool fat), and one or more hydrocarbons like those indicated above, preferably a soft paraffin or a petrolatum, more preferably in combination with liquid paraffin.

A special embodiment of the aforementioned ointment base comprises e.g. 5 to 17 parts by weight of wool fat, and 50 to 65 parts by weight of white petrolatum as well as 20 to 30 parts by weight of liquid paraffin.

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In some embodiments, the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base is selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components. The agent is preferably used in amounts of 1 to 20 percent, more preferably 1 to 10 percent by weight of the entire semisolid ophthalmic composition.

Alcohols having 12 to 20 carbon atoms include particularly stearyl alcohol (C₁₈H₃₇OH), cetyl alcohol (C₁₆H₃₃OH) and mixtures thereof. Preferred are so-called cetostearyl alcohols, mixtures of solid alcohols substantially consisting of stearyl and cetyl alcohol and preferably comprising not less than 40 percent by weight of stearyl alcohol and a sum of stearyl alcohol and cetyl alcohol amounting to at least 90 percent by weight, and compositions comprising not less than 80 percent by weight of cetylstearyl alcohol and an emulsifier, in particular sodium cetostearyl sulfate and/or sodium lauryl sulfate, preferably in amounts not less than 7 percent by weight of emulsifier.

Polyethoxylated castor oils are reaction products of natural or hydrogenated castor oils and ethylene glycol. In some instances, such products are obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:30 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable and preferred is a product commercially available under the trade name Cremophor® EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an nD₂₅=ca. 1.471. Also suitable for use in this category is, for instance, Nikkol® HCO-60, a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0° C.; Freezing point=ca. 32.4° C.; H₂O content (% KF)=ca. 0.03.

Poly(ethylene-glycols) are used in some embodiments as the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base according to the present disclosure. Suitable poly(ethylene-glycols) are typically mixtures of polymeric compounds of the general formula H—(OCH₂-CH₂)_nOH, wherein the index n typically range from 4 to 230 and the mean molecular weight from about 200 to about 10000. Preferably n is a number from about 6 to about 22 and the mean molecular weight between about 300 and about 1000, more preferably n ranges from about 6 to about 13 and the mean molecular weight from about 300 to about 600, most preferably n has a value of about 8.5 to about 9 and the relative molecular weight is about 400. Suitable poly(ethylene-glycols) are readily available commercially, for example poly(ethylene-glycols) having a mean molecular weight of about 200, 300, 400, 600, 1000, 1500, 2000, 3000, 4000, 6000, 8000 and 10000.

The poly(ethylene-glycols), in particular the preferred types described in the foregoing paragraph, are preferably used in amounts of 1 to 10, more preferably 1 to 5 percent by weight of the entire semisolid ophthalmic composition.

An especially preferred embodiment of the compositions according to the instant disclosure comprises an agent for dispersing and/or dissolving of the drug in the ointment base which is selected from a poly(ethylene-glycol), a polyethoxylated castor oil and preferably a mixture of said components.

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Gel/Ointment Viscosity

In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10,000 to about 300,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 15,000 to about 200,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 50,000 to about 150,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 70,000 to about 130,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 90,000 to about 110,000 cps at about 20° C. and shear rate of 1 s⁻¹.

In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 1,000,000 centipoise, between about 750 and 1,000,000 centipoise; between about 1000 and 1,000,000 centipoise; between about 1000 and 400,000 centipoise; between about 2000 and 100,000 centipoise; between about 3000 and 50,000 centipoise; between about 4000 and 25,000 centipoise; between about 5000 and 20,000 centipoise; or between about 6000 and 15,000 centipoise. In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 50,000 and 1,000,000 centipoise.

In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

In some embodiments, the compositions described herein are viscous compositions at body temperature. In some embodiments, viscous compositions contain from about 10% to about 25% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 14% to about 22% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 15% to about 21% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 100,000 cP to about 1,000,000 cP. In

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some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 150,000 cP to about 500,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 250,000 cP to about 500,000 cP. In some of such embodiments, a viscous ophthalmic composition is a liquid at room temperature and gels at about between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42° C.). In some embodiments, a viscous ophthalmic composition is administered as monotherapy for treatment of an ophthalmic disease or condition described herein.

In some embodiments, the viscosity of the gel formulations presented herein is measured by any means described. For example, in some embodiments, an LVDV-II+CP Cone Plate Viscometer and a Cone Spindle CPE-40 is used to calculate the viscosity of the gel formulation described herein. In other embodiments, a Brookfield (spindle and cup) viscometer is used to calculate the viscosity of the gel formulation described herein. In some embodiments, the viscosity ranges referred to herein are measured at room temperature. In other embodiments, the viscosity ranges referred to herein are measured at body temperature (e.g., at the average body temperature of a healthy human).

Gel/Ointment Dose-To-Dose Uniformity

Typical ophthalmic gels are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. Furthermore, typical ophthalmic ointments are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle.

In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

In some cases, described herein include ophthalmic gel compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some cases, described herein include ophthalmic ointment compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

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In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

A nonsettling formulation should not require shaking to disperse drug uniformly. A "no-shake" formulation is potentially advantageous over formulations that require shaking for the simple reason that patients' shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are "no-shake" formulations that maintained the dose-to-dose uniformity described herein.

To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

Methods of Treatment

Disclosed herein are methods of arresting myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above. Also disclosed herein are methods of preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above.

In some embodiments, the ophthalmic aqueous formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous formulation includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic gel formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic ointment formulations described herein are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous formulation described herein is one drop of the aqueous composition from the eye drop bottle. In some embodiments, one dose of

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the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispensing tube.

In some embodiments of the disclosed method, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 2° C., about 3° C., about 4° C., about 5° C., about 6° C., about 7° C., about 8° C., about 9° C., or about 10° C. prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use.

In some embodiments of the disclosed method, the ophthalmic composition is stored at room temperature after first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 16° C. to about 26° C. after to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 16° C., about 17° C., about 18° C., about 19° C., about 20° C., about 21° C., about 22° C., about 23° C., about 24° C., about 25° C., or about 26° C. after to first use.

In some embodiments, the ophthalmic aqueous formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of the aqueous formulation (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic gel formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of gel (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic ointment formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a small amount of ointment (approximately 0.25 inches) was applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years.

In some embodiments, the ophthalmic composition is administered in doses having a dose-to-dose ophthalmic agent concentration variation of less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

The number of times a composition is administered to an individual in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the individual's response to the formulation. In some embodiments, a composition disclosed herein is administered once to an individual in need thereof with a mild acute condition. In some embodiments, a composition

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disclosed herein is administered more than once to an individual in need thereof with a moderate or severe acute condition. In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of an ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the ophthalmic agent is given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is from 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

Once improvement of the patient's ophthalmic conditions has occurred, a maintenance ophthalmic agent dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is optionally reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The amount of ophthalmic agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, according to the particular circumstances surrounding the case, including, e.g., the specific ophthalmic agent being administered, the route of administration, the condition being treated, the target area being treated, and the subject or host being treated. The desired dose is presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals.

In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

Kits/Articles of Manufacture

The disclosure also provides kits for preventing or arresting myopia development. Such kits generally will comprise one or more of the ophthalmic compositions disclosed herein, and instructions for using the kit. The disclosure also contemplates the use of one or more of the ophthalmic compositions, in the manufacture of medicaments for treating, abating, reducing, or ameliorating the symptoms of a

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disease, dysfunction, or disorder in a mammal, such as a human that has, is suspected of having, or at risk for developing myopia.

In some embodiments, kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In other embodiments, the containers are formed from a variety of materials such as glass or plastic.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are also presented herein. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, drop bottles, tubes, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of ophthalmic compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that benefits by controlled release administration of an ophthalmic agent to the eye.

In some embodiments, a kit includes one or more additional containers, each with one or more of various materials (such as rinses, wipes, and/or devices) desirable from a commercial and user standpoint for use of a formulation described herein. Such materials also include labels listing contents and/or instructions for use and package inserts with instructions for use. A set of instructions is optionally included. In a further embodiment, a label is on or associated with the container. In yet a further embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In other embodiments a label is used to indicate that the contents are to be used for a specific therapeutic application. In yet another embodiment, a label also indicates directions for use of the contents, such as in the methods described herein.

In certain embodiments, the ophthalmic compositions are presented in a dispenser device which contains one or more unit dosage forms containing a compound provided herein. In a further embodiment, the dispenser device is accompanied by instructions for administration. In yet a further embodiment, the dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In another embodiment, such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In yet another embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

Example 1—Ophthalmic Formulations

Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-8.

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TABLE 1

Aqueous Solution Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 2

Aqueous Solution Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 3

Aqueous Solution Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.05-0.15	0.005-0.015 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 4

Mucus Penetrating Particle Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution

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TABLE 4-continued

Mucus Penetrating Particle Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Mucus penetrating particles	—	q.s. to formulate atropine at 0.001-0.05 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 5

Mucus Penetrating Particle Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	—	q.s. to formulate atropine at 0.001-0.05 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 6

Cellulose Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine Sulfate	0.01-0.5	0.001-0.05 (wt %)
Viscosity enhancing agent (e.g. hydroxypropyl methylcellulose)	10-50	1-5 (wt %)
Buffer agent and/or pD adjusting agent (e.g., sodium acetate and/or DCl)	—	q.s. for pD = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Deuterated Water	—	q.s. to 100 wt %

TABLE 7

Thermosetting Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Viscosity enhancing agent (e.g. poloxamer 407)	100-250	10-25 (wt %)
Buffer agent and/or pD adjusting agent (e.g., sodium acetate and/or DCl)	—	q.s. for pH = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Deuterated Water	—	q.s. to 100 wt %

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TABLE 8

Ointment Formulation (Atropine Sulfate)		
Ingredient	Quantity (g)	
	for 1000 mL solution	Concentration in 1000 mL aqueous solution
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Dispersing agent (e.g. polyethyleneglycol, and/or polyethoxylated castor oil and/or C12-C20 alcohol	10-200	1-20 (wt %)
Buffering agent pD adjusting agent (e.g. DCl)	—	q.s. for pD = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Ointment base (e.g. wool wax and/or petrolatum and/or liquid paraffin)	—	q.s. to 100 wt %

Example 2—Preparation of an Aqueous Solution
Formulation Containing 0.01% Atropine in D₂O

Stock 1% Solution

In a 100 mL solution, 1 gram of atropine, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) are added along with a quantity sufficient to equal 100 mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

Diluted 0.01% Solution

0.3 mL of the 1% solution was combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 3—Preparation of an Aqueous Solution
Formulation Containing 0.01% Atropine Sulfate

Stock 1% Solution

In a 100 mL solution, 1 gram of atropine sulfate, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) were added along with a quantity sufficient to equal 100 mL sterile water for injection. The solution was mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders had dissolved and the solution became clear with no visible particles. Next, the stir bar was removed, and the solution was poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top was removed from the sterile stock bottle and the stock bottle was capped for storage with a sterile bottle cap.

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Diluted 0.01% Solution

0.3 mL of the 1% solution was combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 4—Stability Analysis

Five 0.01% atropine sulfate solutions were prepared from the 1% atropine sulfate stock solution (preparation as described in Example 2). The pH of the five solutions was 5.87, 5.97, 5.90, 6.24, and 6.16 for solutions 1-5, respectively. Each solution was thoroughly mixed. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers according to Table 9.

TABLE 9

Container Filling Outline		
Type of Container	Volume of 0.01% Atropine Sulfate Drug Product in Container	Total Containers Filled
Sterile Eyedroppers	5-mL	12
Sterile Glass Vials	5-mL	12

The samples were then stored at different conditions for stability analysis. The samples were analyzed at different time points up to 2 months. The storage conditions include: 40° C. with 75% relative humidity (RH) (samples were transferred from 2-8° C. condition after 3 days), 25° C. with 60% RH, and 60° C. The time points were 1 week, 2 weeks, 1 month, and 2 months. At each of the time point, one plastic eyedropper (LDPE plastic) and one glass vial from each of the stored condition were removed and allowed to equilibrate to ambient conditions. Once equilibrated, both the plastic eyedropper and the glass vials were inverted 3 times. The solution in the eyedroppers was transferred to an HPLC vial in a drop wise fashion through the dropper. The solution in the glass vial was aliquotted into an HPLC vial using a glass Pasteur pipette. The samples were then tested for purity and potency using the UPLC method listed in Table 10.

TABLE 10

UPLC Method Parameters	
Parameter	Condition
Column	EMD, Hiber HR PurospherSTAR C-18, 100 × 2.1 mm, 2 μm
Mobile Phase/Diluent	87:13, 50 mM Potassium Phosphate:Acetonitrile, pH 3.5
Flow	Isocratic
Flow Rate	0.5 mL/min
Detection Wavelength	210 nm
Column Temperature	30 ± 3° C.
Autosampler	5 ± 3° C.
Temperature	
Run Time	6.0 minutes
Injection Volume	10 μL*
Needle Wash Solution	90/10 Water:Acetonitrile

*Modified from original method to maintain sensitivity at 100 μg/mL nominal.

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Table 11 lists the stability data for the 0.01% atropine sulfate solutions.

TABLE 11

Stability Data for 0.01% Atropine Sulfate Solutions									
Storage			t = 0			t = 1 week		t = 2 week ¹	
Analyst	Container Type	Condition	Purity	Potency	pH	Purity	Potency	Purity	Potency
1	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.5	99.8	5.9	ND	ND	99.1	99.9
		40° C./75% RH				ND	ND	96.2	97.3
		60° C.				80.8	83.3	86.2	88.6
	Glass Vial	25° C./60% RH	99.8	100.4	ND	ND	ND	92.2	93.1
		40° C./75% RH				ND	ND	73.6	74.1
		60° C.				43.1	43.9	28.3	28.4
	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.7	99.9	6.0	ND	ND	99.1	99.6
		40° C./75% RH				ND	ND	96.6	97.2
		60° C.				89.4	92.2	92.2	94.0
2	Glass Vial	25° C./60% RH	99.8	100.2	ND	ND	ND	92.6	92.9
		40° C./75% RH				ND	ND	74.7	75.1
		60° C.				54.2	55.2	37.3	37.4
	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.3	96.3	5.9	ND	ND	98.7	96.1
		40° C./75% RH				ND	ND	96.7	93.1
		60° C.				88.8	89.0	88.0	86.8
	Glass Vial	25° C./60% RH	99.4	98.4	ND	ND	ND	94.1	91.2
		40° C./75% RH				ND	ND	72.2	74.6
		60° C.				48.6	51.1	34.1	34.9
4	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.8	99.6	6.2	ND	ND	99.1	98.8
		40° C./75% RH				ND	ND	96.3	97.0
		60° C.				90.5	93.0	89.3	90.6
	Glass Vial	25° C./60% RH	99.8	98.8	ND	ND	ND	90.7	90.0
		40° C./75% RH				ND	ND	71.0	68.7
		60° C.				52.4	52.1	29.7	28.6
	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.6	100.5	6.2	ND	ND	99.3	100.4
		40° C./75% RH				ND	ND	95.9	96.7
		60° C.				91.2	94.6	91.4	93.6
5	Glass Vial	25° C./60% RH	99.8	100.7	ND	ND	ND	90.5	91.3
		40° C./75% RH				ND	ND	71.3	71.9
		60° C.				46.3	47.4	29.5	29.6

Storage			t = 1 month ²			t = 2 month ³		
Analyst	Container Type	Condition	Purity	Potency	pH	Purity	Potency	pH
1	Eyedropper, LDPE (Plastic)	25° C./60% RH	ND	ND	ND	95.4	97.4	6.3
		40° C./75% RH	95.1	95.6	5.2	ND	ND	ND
		60° C.	88.3	91.5	4.2	ND	ND	ND
	Glass Vial	25° C./60% RH	80.7	80.5	7.8	73.0	74.5	7.3
		40° C./75% RH	50.1	50.2	7.4	ND	ND	ND
		60° C.	ND	ND	ND	ND	ND	ND
	Eyedropper, LDPE (Plastic)	25° C./60% RH	ND	ND	ND	97.0	99.1	6.1
		40° C./75% RH	95.5	95.8	5.6	ND	ND	ND
		60° C.	90.6	94.4	4.1	ND	ND	ND
2	Glass Vial	25° C./60% RH	82.5	82.2	7.6	80.2	81.6	7.3
		40° C./75% RH	59.1	59.0	7.2	ND	ND	ND
		60° C.	ND	ND	ND	ND	ND	ND
	Eyedropper, LDPE (Plastic)	25° C./60% RH	ND	ND	ND	95.8	94.8	6.3
		40° C./75% RH	94.8	91.8	5.5	ND	ND	ND
		60° C.	88.6	87.7	4.1	ND	ND	ND
	Glass Vial	25° C./60% RH	85.0	81.9	7.5	79.3	78.3	7.3
		40° C./75% RH	61.3	63.0	7.2	ND	ND	ND
		60° C.	ND	ND	ND	ND	ND	ND
4	Eyedropper, LDPE (Plastic)	25° C./60% RH	ND	ND	ND	96.4	97.6	6.3
		40° C./75% RH	94.5	94.2	5.6	ND	ND	ND
		60° C.	84.2	85.8	4.2	ND	ND	ND
	Glass Vial	25° C./60% RH	76.9	75.1	7.6	72.5	71.6	7.4
		40° C./75% RH	57.0	56.7	7.2	ND	ND	ND
		60° C.	ND	ND	ND	ND	ND	ND
	Eyedropper, LDPE (Plastic)	25° C./60% RH	ND	ND	ND	97.8	100.5	6.2
		40° C./75% RH	96.8	97.6	5.5	ND	ND	ND
		60° C.	90.3	92.8	4.2	ND	ND	ND
5	Glass Vial	25° C./60% RH	79.3	79.7	7.8	72.8	74.6	7.3
		40° C./75% RH	56.0	56.4	7.3	ND	ND	ND
		60° C.	ND	ND	ND	ND	ND	ND
		60° C.	ND	ND	ND	ND	ND	ND

¹The 25° C. and the 60° C. samples were pulled at 15 days, the 40° C. samples were pulled at 11 days.

²The 25° C. and the 60° C. samples were pulled at 28 days, the 40° C. samples were pulled at 24 days.

³The 25° C. and the 60° C. samples were pulled at 46 days.

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A change in the pH of the 0.01% Atropine Sulfate solutions was observed over the course of the stability study. The plastic (LDPE) eyedroppers maintained pH around 6.2 when stored at 25° C. for 2 months. However at the same time point, the pH of the 0.01% atropine has increased to 7.2 when stored in glass vials. Additionally, when stored at elevated temperatures (e.g. 40° C. and 60° C.), the pH in the plastic (LDPE) eyedroppers dropped to approximately 4-5, while the pH maintained around 7.2 when stored in the glass vials.

There was also a significant difference in the rate of degradation for Atropine Sulfate (0.01%) when stored in plastic (LDPE) eyedroppers versus Type I glass vials. However, in both containers there was an increase of an early eluting related substance at relative retention time (RRT) =0.87-0.89. In some cases, this early eluting related substance is referred to as primary degradant. In some instances, the primary degradant is referred to as RRT 0.87-0.89. This related substance is likely to be the first parameter to fail specification regardless of the container. The amount of this related substance was tracked at each time point and is listed in Table 12.

TABLE 12

Area (%) of the Main Degradation Species for 0.01% Atropine Sulfate (RRT 0.87-0.89)						
Analyst	Temperature ° C.	t = 0	t = 1 week	t = 2 week	t = 1 month	t = 2 months
1	25	0.08	NA	0.92	NA	3.98
	40	NA	NA	3.74	4.78	NA
	60	NA	17.78	13.49	11.51	NA
2	25	0.07	NA	0.88	NA	2.46
	40	NA	NA	3.26	4.37	NA
	60	NA	9.38	7.67	9.13	NA
3	25	0.07	NA	1.05	NA	2.88
	40	NA	NA	2.98	4.85	NA
	60	NA	9.59	11.57	10.55	NA
4	25	0.08	NA	0.92	NA	3.09
	40	NA	NA	3.43	5.32	NA
	60	NA	8.30	10.46	15.49	NA
5	25	0.08	NA	0.64	NA	1.66
	40	NA	NA	3.96	3.07	NA
	60	NA	7.61	8.35	9.7	NA
Average 25° C.		0.08	NA	0.88	NA	2.81
Average 40° C.		NA	NA	3.47	4.48	NA
Average 60° C.		NA	10.53	10.31	11.28	NA

Arrhenius based shelf life predictions were calculated using the related substance data from Table 12. These predictions are based on an assumption that the degradation is first order (linear). These predictions are illustrated in FIGS. 1 and 2. FIG. 1 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 40° C. The pH range of the atropine sulfate solution is from 5.9-6.2. FIG. 2 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 60° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

Example 5—1% Atropine Sulfate (Bausch+Lomb) Sample Analysis

The 1% atropine sulfate sample was obtained from Bausch+Lomb (Lot 198421). For comparison the pH of the 1% Atropine Sulfate drug product was determined in the neat solution as well as a sample that was diluted to the current nominal concentration (0.01% Atropine Sulfate)

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using the vehicle. Additionally a sample was diluted to the nominal concentration with method diluent. Both samples diluted to the nominal concentration were analyzed using the RP-UPLC method (Table 10). The results are listed in Table 13.

TABLE 13

pH and Purity of the Bausch + Lomb Atropine Sulfate Sample		
Sample	pH	Purity (% area)
1% Atropine Sulfate	4.89	ND
0.01% Atropine Sulfate, diluted with Vehicle	6.16	99.6%
0.01% Atropine Sulfate, diluted with Diluent	ND	99.6%
Vehicle	7.94	ND

ND = not determined

Example 6—Dose Uniformity (10-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 10 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 7—Dose Uniformity (5-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 5 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 8—Dose Uniformity (2-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 2 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 9—Formulation Stability Comparison

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Eight formulations illustrated in Table 14A were analyzed at t=0, 2 weeks, and 4 weeks. A RP-HPLC method was used to carry out the analysis.

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TABLE 14A

Atropine sulfate formulations							
Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	—	4.2	SWFI
2	0.025	0.01	0.90	0.01	—	4.2	SWFI
3	0.010	0.01	0.90	0.01	—	4.8	SWFI
4	0.025	0.01	0.90	0.01	—	4.8	SWFI
5	0.010	0.01	0.90	—	0.04	5.8	SWFI
6	0.025	0.01	0.90	—	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	—	5.2	D ₂ O
8	0.010	0.01	0.90	—	0.04	6.2	D ₂ O

The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware. The pD of Formulation 7 and Formulation 8 are 5.2 and 6.2, respectively. In some instances, the pD is calculated as $pD=0.4+pH^*$, in which pH^* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

Table 14B illustrates analysis time points for the formulations listed in Table 14A.

TABLE 14B

Schedule for atropine sulfate formulation testing			
Storage Condition (Horizontal)	Time Point		
	Initial (t = 0)	2 Week	4 Week
25° C./60% RH	X	X	X
40° C./75% RH		X	X
60° C.		X	X

Table 15 illustrates the atropine sulfate purity data associated with each of the eight formulations. Purity is indicated as percentage of area under the curve.

TABLE 15

Atropine sulfate purity as Area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks ¹
Formulation 1 pH 4.2	25/60	97.39	97.76	98.20
	40/75		97.25	97.04
	60° C.		94.98	93.87
Formulation 2 pH 4.2	25/60	98.85	99.03	99.08
	40/75		98.50	98.32
	60° C.		97.47	96.65
Formulation 3 pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60° C.		95.94	94.65
Formulation 4 pH 4.8	25/60	98.81	98.75	98.46
	40/75		98.26	98.01
	60° C.		96.22	94.04
Formulation 5 pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60° C.		80.94	66.83
Formulation 6 pH 5.8	25/60	99.08	98.91	98.46
	40/75		97.65	96.20
	60° C.		89.15	80.68
Formulation 7 pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60° C.		96.70	94.01

TABLE 15-continued

Atropine sulfate purity as Area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks ¹
Formulation 8 pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60° C.		95.97	92.72

¹Some chromatographic interference were observed to occur late in the run (~27-32 minutes) for many of the t = 4 week stability samples and in some instances is proposed to be system related.

After four weeks of storage at 60° C., in some instances the atropine sulfate concentration have an impact on the stability for the formulations containing acetic acid at pH 4.2. For example, atropine sulfate concentration at 0.025% w/v (Formulation 2) showed a 2.8% increase in % purity at pH 4.2 compared to the atropine sulfate concentration at 0.010% w/v (Formulation 1). This trend was not observed for the acetic acid formulations at pH 4.8 (Formulations 3 and 4); rather a 0.6% decrease in % purity was observed for the higher doses.

The dose dependent stability trend that was observed at pH=4.2 was also seen in the formulations containing citric acid at pH 5.8 (Formulations 5 and 6). After four weeks of storage at 60° C. there is approximately 14% less degradation in the higher doses than observed in the lower dose.

At both the high and the low doses, more degradation is observed in the formulations that start at a higher pH. This degradation is predominantly the growth of tropic acid. In some instances, buffer species plays a role in the observed degradation between the different pH values.

The percentage of tropic acid observed for each of the formulations at t=4 weeks and at 60° C. are as follow:

Formulation 1—Tropic acid observed is 0.54%.

Formulation 2—Tropic acid observed is 0.93%.

Formulation 3—Tropic acid observed is 1.58%.

Formulation 4—Tropic acid observed is 3.03%.

Formulation 5—Tropic acid observed is 29.13%.

Formulation 6—Tropic acid observed is 16.84%.

Formulation 7—Tropic acid observed is 1.07%.

Formulation 8—Tropic acid observed is 4.03%.

In some embodiments, switching the water source to deuterated water (D₂O) has an impact on stabilizing the growth of the tropic acid peak for the formulation containing acetic acid at pD 5.2 (Formulation 7), see FIG. 4. In addition, in the formulation containing citric acid at pD 6.2 (Formulation 8), the deuterated water also stabilizes atropine sulfate, see FIG. 5.

Table 16 illustrates tropic acid as area under the curve for each of the eight formulations. Tropic acid is a degradant of

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atropine sulfate. In some instances, LOQ was previously found to be 0.05% for the RP-HPLC method.

TABLE 16

Tropic acid as area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 pH 4.2	25/60	<LOQ	0.08	<LOQ
	40/75		0.10	0.10
	60° C.		0.37	0.51
Formulation 2 pH 4.2	25/60	<LOQ	0.05	<LOQ
	40/75		0.11	0.12
	60° C.		0.46	0.93
Formulation 3 pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60° C.		0.90	1.58
Formulation 4 pH 4.8	25/60	<LOQ	0.10	0.13
	40/75		0.31	0.53
	60° C.		1.84	3.03
Formulation 5 pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60° C.		16.62	29.13
Formulation 6 pH 5.8	25/60	<LOQ	0.24	0.42
	40/75		1.30	2.44
	60° C.		9.32	16.84
Formulation 7 pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60° C.		0.71	1.07
Formulation 8 pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60° C.		2.32	4.03

Table 17 illustrates percentage of potency of atropine in the eight formulations.

TABLE 17

% Potency				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 pH 4.2	25/60	109.4	110.3	112.8
	40/75		111.0	112.4
	60° C.		112.8	114.8
Formulation 2 pH 4.2	25/60	102.9	107.1	109.7
	40/75		108.4	109.6
	60° C.		109.4	111.0
Formulation 3 pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60° C.		108.0	109.9
Formulation 4 pH 4.8	25/60	102.5	107.9	109.2
	40/75		107.4	108.9
	60° C.		107.9	108.8
Formulation 5 pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60° C.		90.2	77.7
Formulation 6 pH 5.8	25/60	107.2	107.1	109.1
	40/75		106.8	107.1
	60° C.		99.0	93.7
Formulation 7 pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60° C.		111.8	113.5
Formulation 8 pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60° C.		101.6	103.0

After 4 weeks of storage, the observed potency values were elevated from the t=0 and 2 week time points, with the exception of Formulations 5 and 6 at 60° C. where the potencies dropped due to degradation. In some instances, these potency values are within the error of the HPLC method, but appear to be trending upward. Mass balance was calculated for the 60° C. data and results were consistent across the formulations and levels of degradation, although skewed lower due to the higher than anticipated potency values at 4 weeks, see FIG. 3.

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Table 18 illustrates pH or pD stability of the eight formulations.

TABLE 18

pH/pD Stability				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 (pH)	25/60	4.21	3.93	4.02
	40/75		3.86	3.96
	60° C.		3.71	3.86
Formulation 2 (pH)	25/60	4.26	4.11	4.25
	40/75		4.04	4.17
	60° C.		3.93	4.10
Formulation 3 (pH)	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60° C.		4.32	4.40
Formulation 4 (pH)	25/60	4.98	4.93	5.05
	40/75		4.89	4.98
	60° C.		4.77	4.77
Formulation 5 (pH)	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60° C.		5.82	5.78
Formulation 6 (pH)	25/60	5.80	5.69	5.77
	40/75		5.65	5.67
	60° C.		5.54	5.50
Formulation 7 (pD)	25/60	5.31	5.10	5.24
	40/75		5.08	5.15
	60° C.		5.00	4.93
Formulation 8 (pD)	25/60	6.25	5.72	5.88
	40/75		5.74	5.78
	60° C.		5.58	5.50

The italicized values are pD values for a deuterated sample. In some embodiments, the pD of the deuterated samples are $pD = pH_{reading} + 0.4$ (Glasoe, et al. "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

At the two lower temperatures, the pH values at t=4 week are slightly elevated from the t=2 week time point. These data were generated using a new glass pH probe. In some instances, the observed differences are due to the probe differences or additional variables such as for example, the age of the standard buffers or temperature gradients within the laboratory environment. The downward pH trend for each formulation with increasing temperatures at t=4 week is consistent with previous data and is consistent with the increase in the amount of tropic acid present in the stability sample.

Example 10—Determination of Shelf Life and Activation Energy

Activation energy was calculated for the eight formulations disclosed in Example 9 and comparison with a reference standard was made with Formulations 4-7.

Table 19 illustrates the activation energy (Ea) calculation. The Ea minimum is 17.8 Kcal/mol, the Ea maximum is 21.3 Kcal/mol, and the Ea mean is 19.5 Kcal/mol. Mean is $\pm 3 \times \text{stdev}$. FIGS. 6 and 7 illustrate the poor correlation between RS and tropic acid with Formulation 4 and Formulation 7, respectively. FIGS. 8 and 9 illustrate improved correlation between RS and tropic acid with Formulation 5 and Formulation 6, respectively. At a lower pH (e.g. pH 4.8 or lower), there was a poor correlation observed (Formulation 4 and Formulation 7). This was due to a slowed hydrolysis and increased alternative degradation pathways. At a higher pH (e.g., pH 5.8 or higher), an improved or better correlation was observed (Formulation 5 and Formulation 6). This was due to the hydrolysis of atropine as the primary degradant. It is noted that the activation energy is for the

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specific acid catalyzed degradation to tropic acid—the predominant degradation product and degradation mechanism operating at pH 5.8 or higher.

TABLE 19

Activation energy for total related substance (RS) and tropic acid.		
	Total RS	Tropic Acid
1	Poor	Poor
2	12.2	Poor
3	Poor	18.3
4	16.8	18.1
5	19.8	19.7
6	19.2	20.0
7	13.2	15.5
8	Poor	18.9
Mean	16.2	18.4
Stdev	3.4	1.6
RSD	21%	9%

Table 20 illustrates the rate of RS or tropic acid formation per week at 40° C.

TABLE 20

Formulation	Rate 40° C. (total RS %/wk)	Rate 40° C. (Tropic acid %/wk)
Formulation 5	0.01% Atr Citrate pH 5.8	1.16
Formulation 6	0.025% Atr Citrate pH 5.8	0.72
Formulation 8	0.01% Atr Citrate pD 6.2 D ₂ O	0.163

Table 21 illustrates the activation energy and predicted shelf life at 30° C. calculated based on Table 20. It is assumed for the calculation that tropic acid and total RS is 5% (self-life).

TABLE 21A

Formulation	Rate @30° C. (Total RS %/wk)			Estimated Shelf life @30° C. (mo)		
	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.45	0.41	0.38	2.78	3.04	3.33
6	0.28	0.26	0.23	4.47	4.90	5.37
8	—	—	—	—	—	—

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TABLE 21B

Formulation	Rate @30° C. (Tropic acid %/wk)			Estimated Shelf life @30° C. (mo)		
	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.42	0.39	0.35	2.95	3.24	3.54
6	0.24	0.22	0.20	5.28	5.78	6.33
8	0.06	0.06	0.05	19.75	21.64	23.70

At pD 6.2, the deuterated formulation (Formulation 8) has a predicted shelf life of close to 2 years at 30° C.

Table 22 illustrate the predicted shelf life at temperatures of 40° C., 30° C., 25° C., and 2-8° C. for Formulations 4-8 for total RS and tropic acid, respectively.

TABLE 22

Stability Prediction						
Formulation	Temperature (° C.)	RS		Temperature (° C.)	Tropic Acid	
		weeks	months		weeks	months
4	40	16.5	4.1	40	7.7	1.9
	30	40.2	10.1	30	20.0	5.0
	25	64.2	16.0	25	33.0	8.3
5	2-8	493.4	123.4	2-8	296.8	74.2
	40	2.8	0.7	40	0.9	0.2
	30	7.9	2.0	30	2.7	0.7
6	25	13.7	3.4	25	4.6	1.2
	2-8	151.1	37.8	2-8	50.5	12.6
	40	5.8	1.4	40	1.7	0.4
7	30	15.9	4.0	30	4.8	1.2
	25	27.3	6.8	25	8.4	2.1
	2-8	281.6	70.4	2-8	95.9	24.0
8	40	11.5	2.9	40	16.9	4.2
	30	23.2	5.8	30	38.4	9.6
	25	33.4	8.4	25	59.1	14.8
8	2-8	165.7	41.4	2-8	388.2	97.1
	40	—	—	40	6.2	1.6
	30	—	—	30	17.0	4.3
8	25	—	—	25	28.9	7.2
	2-8	—	—	2-8	287.1	71.8

Example 11—Additional Formulation Stability Comparison

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Thirteen formulations illustrated in Table 23A were analyzed. Formulations 1-8 had been analyzed at t=0, 2 weeks, 4 weeks, and 8 weeks. Formulations 9-13 had been analyzed at t=0, 2 weeks, and 4 weeks. The pH values reported herein are the measured pH values obtained using the Thermo Scientific, Orion Dual Star pH/ISE benchtop pH meter and the Orion Double Junction Micro pH probe S/N 501-18520 calibrated with H₂O based standards.

TABLE 23A

Atropine sulfate Formulations							
Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	—	4.2	SWFI
2	0.025	0.01	0.90	0.01	—	4.2	SWFI
3	0.010	0.01	0.90	0.01	—	4.8	SWFI
4	0.025	0.01	0.90	0.01	—	4.8	SWFI
5	0.010	0.01	0.90	—	0.04	5.8	SWFI

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TABLE 23A-continued

Atropine sulfate Formulations							
Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
6	0.025	0.01	0.90	—	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	—	5.2	D ₂ O
8	0.010	0.01	0.90	—	0.04	(pD) 6.2	D ₂ O
9	0.010	—	0.90	—	0.04	(pD) 6.8	D ₂ O
10	0.010	—	0.90	—	0.04	6.4	H ₂ O (control)
11	0.010	—	0.90	—	0.08	6.4	H ₂ O (control)
12	0.010	—	0.90	—	0.04	7.2	D ₂ O
13	0.010	—	0.90	—	0.04	(pD) 6.8	H ₂ O (control)

The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware and filled into LDPE eye droppers. In some instances, the pD is calculated as $pD=0.4+pH^*$, in which pH^* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

Table 23B illustrates analysis time points for the formulations listed in Table 23A.

TABLE 23B

Schedule for atropine sulfate formulation testing			
Storage	Time Point		
Condition (Horizontal)	Initial (t = 0)	2 Week	4 Week
25° C./60% RH	X	X	X
40° C./75% RH		X	X
60° C.		X	X

Table 24A and Table 24B illustrate atropine sulfate purity data associated with the atropine sulfate formulations. Purity is indicated as percentage of area under the curve. The T & indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 24A

Atropine Sulfate Purity as Area-% for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	98.16	98.16	98.45
↓A H ₂ O pH 4.8	40/75		97.98	97.35
	60° C.		95.94	94.65
Formulation 5	25/60	98.16	97.92	97.54
↓C H ₂ O pH 5.8	40/75		95.88	93.51
	60° C.		80.94	66.83
Formulation 10	25/60	98.66	96.67	95.81
↓C H ₂ O pH 6.4	40/75		91.07	85.27
	60° C.		59.77	42.87
Formulation 11	25/60	99.47	97.87	96.69
↓C(2x) H ₂ O pH 6.4	40/75		90.97	84.26
	60° C.		54.96	34.40
Formulation 13	25/60	97.21	95.42	93.24
↓C H ₂ O pH 6.8	40/75		83.05	73.00
	60° C.		43.99	27.50

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TABLE 24B

Atropine Sulfate Purity as Area-% for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	98.93	99.07	98.39
↓A D ₂ O pD 5.2	40/75		98.51	97.55
	60° C.		96.70	94.01
Formulation 8	25/60	98.93	98.95	98.51
↓C D ₂ O pD 6.2	40/75		98.53	97.44
	60° C.		95.97	92.72
Formulation 9	25/60	99.29	98.42	98.07
↓C D ₂ O pD 6.8	40/75		95.20	93.22
	60° C.		75.17	65.97
Formulation 12	25/60	98.53	97.17	95.99
↓C D ₂ O pD 7.2	40/75		90.75	84.64
	60° C.		56.78	46.05

Table 25A and Table 25B illustrate tropic acid formation associated with the atropine sulfate formulations. Tropic acid is a degradant of atropine sulfate, and is indicated as percentage of area under the curve. LOQ was found to be 0.05% for the RP-HPLC method. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid, respectively.

TABLE 25A

Tropic Acid as Area-% for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	<LOQ	0.12	0.05
↓A H ₂ O pH 4.8	40/75		0.19	0.27
	60° C.		0.90	1.58
Formulation 5	25/60	<LOQ	0.40	0.71
↓C H ₂ O pH 5.8	40/75		2.22	4.35
	60° C.		16.62	29.13
Formulation 10	25/60	0.74	1.90	3.21
↓C H ₂ O pH 6.4	40/75		7.61	13.49
	60° C.		37.44	54.06
Formulation 11	25/60	0.09	1.31	2.64
↓C(2x) H ₂ O pH 6.4	40/75		7.61	14.68
	60° C.		42.43	62.23
Formulation 13	25/60	2.21	3.66	6.11
↓C H ₂ O pH 6.8	40/75		15.47	25.80
	60° C.		53.24	69.34

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TABLE 25B

Tropic Acid as Area-% for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	<LOQ	0.07	0.08
↓A D ₂ O pD 5.2	40/75		0.14	0.24
	60° C.		0.71	1.07
Formulation 8	25/60	<LOQ	0.11	0.14
↓C D ₂ O pD 6.2	40/75		0.33	0.65
	60° C.		2.32	4.03
Formulation 9	25/60	0.06	0.55	1.06
↓C D ₂ O pD 6.8	40/75		3.16	6.29
	60° C.		21.09	29.25
Formulation 12	25/60	0.42	1.35	2.62
↓C D ₂ O pD 7.2	40/75		7.27	13.53
	60° C.		38.58	48.15

Table 26A and Table 26B illustrate the percentage of potency of atropine in the formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 26A

Percentage of potency for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	106.3	108.0	109.6
↓A H ₂ O pH 4.8	40/75		108.1	110.0
	60° C.		108.0	109.9
Formulation 5	25/60	105.0	105.9	107.1
↓C H ₂ O pH 5.8	40/75		103.8	103.5
	60° C.		90.2	77.7
Formulation 10	25/60	101.7	100.0	98.0
↓C H ₂ O pH 6.4	40/75		89.4	87.0
	60° C.		63.7	45.7
Formulation 11	25/60	97.5	96.1	94.3
↓C(2x) H ₂ O pH 6.4	40/75		89.4	82.0
	60° C.		55.7	35.20
Formulation 13	25/60	99.4	96.9	94.1
↓C H ₂ O pH 6.8	40/75		85.0	74.0
	60° C.		46.4	29.8

TABLE 26B

Percentage of potency for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	107.3	111.3	112.9
↓A D ₂ O pD 5.2	40/75		111.6	113.5
	60° C.		111.8	113.5
Formulation 8	25/60	99.0	103.0	105.0
↓C D ₂ O pD 6.2	40/75		104.9	104.7
	60° C.		101.6	103.0
Formulation 9	25/60	101.4	99.9	100.1
↓C D ₂ O pD 6.8	40/75		97.4	93.2
	60° C.		78.7	68.9
Formulation 12	25/60	104.9	103.5	101.6
↓C D ₂ O pD 7.2	40/75		96.9	89.1
	60° C.		62.5	50.9

Table 27A and Table 27B illustrate the stability of pH or pD for the atropine sulfate formulations. The T & indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

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TABLE 27A

Stability of pH for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	4.85	4.44	4.61
↓A H ₂ O pH 4.8	40/75		4.41	4.54
	60° C.		4.32	4.40
Formulation 5	25/60	5.87	5.93	6.03
↓C H ₂ O pH 5.8	40/75		5.96	5.96
	60° C.		5.82	5.78
Formulation 10	25/60	6.43	6.41	6.46
↓C H ₂ O pH 6.4	40/75		6.62	6.67
	60° C.		6.01	5.92
Formulation 11	25/60	6.44	6.47	6.72
↓C(2x) H ₂ O pH 6.4	40/75		6.66	6.61
	60° C.		6.27	6.23
Formulation 13	25/60	6.77	6.91	6.91
↓C H ₂ O pH 6.8	40/75		6.65	6.62
	60° C.		6.30	6.19

TABLE 27B

Stability of pD for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	5.31	5.10	5.24
↓A D ₂ O pD 5.2	40/75		5.08	5.15
	60° C.		5.00	4.93
Formulation 8	25/60	6.25	5.72	5.88
↓C D ₂ O pD 6.2	40/75		5.74	5.78
	60° C.		5.58	5.50
Formulation 9	25/60	6.76	6.80	6.81
↓C D ₂ O pD 6.8	40/75		6.78	6.86
	60° C.		6.45	6.24
Formulation 12	25/60	7.25	7.18	7.26
↓C D ₂ O pD 7.2	40/75		7.14	7.15
	60° C.		6.52	6.36

Example 12. Determination of Shelf Life and Activation Energy for Atropine Sulfate Formulations of Example 11

Activation energy was calculated for the atropine sulfate formulations disclosed in Example 11. Specifically, activation energies were calculated from the total % of related substances (RS) at 40° C. and 60° C. (2 point calculations) and from tropic acid formation at 40° C. and 60° C. (2 point calculations). These values were then averaged. Table 28 illustrates the activation energy calculation. Table 29 illustrates estimated shelf-lives from the 40° C. rate of formation of % RS and tropic acid, respectively. FIG. 10 illustrates estimated shelf lives for D₂O and H₂O formulations.

TABLE 28

Activation Energy		
Atropine Formulations	Total RS	Tropic Acid
7	14	19
3	16	17
8	20	21
5	14	Poor Corr
6	15	16
Mean	16.3	18.7
Stdev	2.68	1.90
RSD	16%	10%
Poor Corr:	One or more curve had R ² <0.95	

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TABLE 29

Estimated Shelf Life				
Formulation	Estimated Shelf life/mo			
	Total related substances % (limit = 8%)		Tropic acid % (limit = 5%)	
	8° C.	25° C.	8° C.	25° C.
0.01% w/v Atr	189	26	1427	147
0.01% w/v Acetate				
0.9% w/v NaCl				
0.01% w/v BAK				
pD 5.2 D ₂ O (Formulation 7)				
0.01% w/v Atr	211	29	1095	113
0.01% w/v Acetate				
0.9% w/v NaCl				
0.01% w/v BAK				
pH4.8 H ₂ O (Formulation 3)				
0.01% w/v Atr	158	22	369.8	38
0.04% w/v Citrate				
0.9% w/v NaCl				
0.01% w/v BAK				
pD 6.2 D ₂ O (Formulation 8)				
0.01% w/v Atr	37	5.2	54	5.5
0.04% w/v Citrate				
0.9% w/v NaCl				
0.01% w/v BAK				
pH5.8 H ₂ O (Formulation 5)				
0.01% Atr	13.6	2.6		
0.9% w/v NaCl				
pH5.9 H ₂ O extemporaneous preparation				

Table 30 illustrates the predicted shelf life at temperatures of 40° C., 30° C., 25° C., and 2-8° C. for Formulations 2-8 for total RS and tropic acid, respectively.

TABLE 30

Stability Prediction						
Formulation	Temperature (° C.)	RS		Temperature (° C.)	Tropic Acid	
		weeks	months		weeks	months
2	40	64.5	16.1	40	—	—
	30	153.2	38.3	30	—	—
	25	241.2	60.3	25	—	—
	2-8	1747.9	437.0	2-8	—	—
3	40	31.1	7.8	40	99.5	24.9
	30	73.9	18.5	30	268.3	67.1
	25	116.3	29.1	25	451.8	113.0
	2-8	842.9	210.7	2-8	4382.0	1095.5
4	40	30.7	7.7	40	42.1	10.5
	30	73.0	18.2	30	113.7	28.4
	25	114.9	28.7	25	191.5	47.9
	2-8	832.6	208.1	2-8	1857.0	464.2
5	40	5.5	1.4	40	4.9	1.2
	30	13.1	3.3	30	13.2	3.3
	25	20.6	5.2	25	22.2	5.5
	2-8	149.3	37.3	2-8	215.0	53.8

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TABLE 30-continued

Stability Prediction						
Formulation	Temperature (° C.)	RS		Temperature (° C.)	Tropic Acid	
		weeks	months		weeks	months
6	40	10.7	2.7	40	8.8	2.2
	30	25.5	6.4	30	23.7	5.9
	25	40.1	10.0	25	39.8	10.0
	2-8	290.5	72.6	2-8	386.5	96.6
7	40	27.9	7.0	40	129.6	32.4
	30	66.4	16.6	30	349.6	87.4
	25	104.5	26.1	25	588.7	147.2
	2-8	757.3	189.3	2-8	5709.4	1427.4
8	40	23.3	5.8	40	33.6	8.4
	30	55.3	13.8	30	90.6	22.6
	25	87.2	21.8	25	152.5	38.1
	2-8	631.6	157.9	2-8	1479.2	369.8

Example 13—Forced Degradation Study of Atropine Formulation 8 in D₂O and H₂O Conditions

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) was used for this experiment. A correction factor of 83.3% is used to quantitate amount of free Atropine. Table 31 shows the D₂O and H₂O formulation compositions.

TABLE 31

Formulation 8 Compositions		
Formulation	[Free Atropine] (μg/mL)	Composition
8 - D ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in D ₂ O, pD 6.2
8 - H ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in H ₂ O, pH 5.8

D₂O-based Formulation 8 and H₂O-based Formulation 8 were subjected to acid, base, light, heat and oxidative stress. Approximately 5-20% degradation was targeted for all stress conditions to produce sufficient degradation while avoiding secondary degradation. At each condition, Formulation 8 samples were incubated alongside a vehicle control containing BAK. For the light condition, a foil wrapped Formulation 8 control and foil wrapped vehicle control were prepared to understand if extraneous degradation, such as heat in the light box, were to occur. A RP-HPLC method was used to carry out the analysis. Mass balance (the correlation of potency and purity by area-%) was also evaluated using Equation 1.

$$\text{Mass Balance} = \frac{(\text{Potency}_{\text{initial}} + (100 - \text{Purity}_{\text{initial}}))}{(\text{Potency}_{\text{final}} + (100 - \text{Purity}_{\text{final}}))}$$

The forced degradation results were processed at 210 nm, and are presented in Tables 32A and 32B for H₂O and D₂O formulations, respectively.

TABLE 32A

Forced Degradation Results for Formulation 8-H ₂ O							
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Control 2-8° C., foil wrapped	3 day	100.9	100.0	0.412	0.657	Y	

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TABLE 32A-continued

Forced Degradation Results for Formulation 8-H ₂ O								
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance	
Acid (1.0N HCl)	Ambient, foil wrapped	23 day	-7.9	-5.9	0.301	0.513	Y	101.8%
Base (0.001N NaOH)	Ambient, foil wrapped	4 hr	-5.2	-6.6	0.417	0.725	Y	98.7%
Heat	60° C., foil wrapped	6 hr	-7.3	-7.9	0.462	0.741	Y	99.5%
		7 day	-12.1	-11.9	0.428	0.478	Y	100.3%
		10 day	-18.4	-18.4	0.476	0.752	Y	100.0%
Light	Ambient, clear glass vial	1.1 million lux hours (10 day)	-10.1	-7.6	0.478	0.831	Y	102.5%
		1.5 million lux hours (14 day)	-19.1	-12.2	0.597	0.911	Y	107.1%
Light Control	Ambient, foil wrapped	1.1 million lux hours (10 day)	-0.4	-0.5	0.411	0.665	Y	99.9%
		1.5 million lux hours (14 day)	-3.0	-0.3	0.388	0.592	Y	102.8%
Oxidation (3% H ₂ O ₂)	Ambient, foil wrapped	3 day	-16.0	-7.9	0.532	0.791	Y	108.8%
		4 day	-28.0	-13.9	0.473	0.777	Y	115.7%
		7 day	-29.4	-13.5	0.705	0.967	Y	118.9%

TABLE 32B

Forced Degradation Results for Formulation 8-D ₂ O								
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance	
Control	2-8° C., foil wrapped	4 day	106.7	98.3	0.361	0.659	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	17 day	-6.9	-5.5	0.250	0.469	Y	97.9%
Base (0.001N NaOH)	Ambient, foil wrapped	5 day	-2.3	-2.2	0.495	0.849	Y	100.0%
Base (0.005N NaOH)	Ambient, foil wrapped	30 min	-9.7	-9.6	0.601	0.894	Y	100.2%
Heat	60° C., foil wrapped	17 day	-18.1	-16.9	0.281	0.550	Y	101.1%
Light	Ambient, clear glass vial	0.44 million lux hours (4 day)	-14.1	-4.5	0.463	0.733	Y	109.6%
		0.87 million lux hours (8 day)	-24.2	-11.3	0.528	0.846	Y	113.8%
Light Control (foil covered)	Ambient, foil wrapped	0.44 million lux hours (4 day)	-0.2	1.7	0.354	0.640	Y	101.8%
		0.87 million lux hours (8 day)	0.0	1.4	0.330	0.599	Y	101.3%

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TABLE 32B-continued

Forced Degradation Results for Formulation 8-D ₂ O								
Stress Condition		Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Oxidation (3% H ₂ O ₂)	Ambient,	4 day	-10.6	-3.0	0.439	0.720	Y	107.5%
	foil	8 day	-17.9	-8.3	0.385	0.672	Y	109.9%
	wrapped							

Example 14—Formulation 8 Stability Comparison

The long-term stability of atropine sulfate formulation 8 in D₂O (see Table 31 for formulation composition) was analyzed at three different storage conditions. Table 33 illustrates the stability criteria: appearance, potency, tropic acid level, total purity, and pD at storage conditions of 25° C. with 60% humidity, 40° C. with 75% humidity, and 60° C. As discussed above, pD=pH_{reading}+0.4 (Glasoe, et al. "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

42.8% of tropic acid was observed in the H₂O formulation while only 6.01% of tropic acid was observed in the D₂O formulation by week 8.

Example 15—Effect of pH on Ophthalmic Acceptance in Guinea Pigs

A cohort of guinea pigs is administered 50 µL of ophthalmic formulations having different pH values described herein. For example, ophthalmic formulations comprising H₂O or deuterated water (e.g., D₂O) are administered to the

TABLE 33

Formulation 8 Stability							
Parameter	Initial	2 weeks	4 weeks	8 weeks	6 months	9 months ²	12 months ³
Storage Condition: 25° C./60% RH							
Appearance		Clear Colorless Solution Free of Particulates					
Potency (Assay)	99.2%	103.0%	105.0%	96.0%	99.7%	97.7%	101.7%
Tropic Acid Level	0.05%	0.11%	0.14%	0.23%	0.55%	0.91%	1.24%
Total Purity ¹	98.9%	98.9%	98.5%	98.1%	99.2%	98.4%	97.8%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.9 (pH 5.5)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.7 (pH 5.3)	5.8 (pH 5.4)
Storage Condition: 40° C./75% RH							
Appearance		Clear Colorless Solution Free of Particulates					
Potency (Assay)	99.2%	104.8%	104.7%	94.9%	96.6%	94.2%	95.6%
Tropic Acid Level	0.05%	0.34%	0.65%	1.24%	3.32%	5.05%	6.71%
Total Purity ¹	98.9%	98.5%	97.5%	96.6%	96.3%	92.5%	90.5%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.6 (pH 5.2)	5.7 (pH 5.3)	5.5 (pH 5.1)	5.7 (pH 5.3)
Storage Condition: 60° C.							
Appearance		Clear Colorless Solution Free of Particulates					
Potency (Assay) ⁴	99.2%	101.6%	103.0%	92.9%	100.6%	104.0%	115.9%
Tropic Acid Level	0.05%	2.33%	4.02%	6.01%	10.33%	10.87%	12.97%
Total Purity ¹	98.9%	96.0%	92.8%	88.8%	85.5%	78.0%	72.4%
pD	6.3 (pH 5.9)	5.6 (pH 5.2)	5.5 (pH 5.1)	5.2 (pH 4.8)	5.1 (pH 4.7)	4.9 (pH 4.5)	5.0 (pH 4.6)

¹Slight variability is observed in the total purity results due to sensitivity differences from one HPLC system to the next.

²Results reported are from a second aliquot taken from the original assay eyedropper.

³Results reported are from an aliquot taken from the original assay eyedropper.

⁴A growing unknown related substance peak is observed to co-elute with the main peak and is included in the Atropine Sulfate potency result due to a lack of a clear inflection point between the two species upon integration.

A comparison of Formula 8 in H₂O and D₂O under three storage conditions is further illustrated in FIG. 11. FIG. 11A shows the presence of tropic acid degradant at 25° C. with 60% humidity. By week 8, about 1.45% of tropic acid was observed in the H₂O formulation while only 0.23% of tropic acid was observed in the D₂O formulation. Similarly, at 40° C. with 75% humidity storage condition (FIG. 11B), 8.34% of tropic acid was observed in the H₂O formulation while only 1.24% of tropic acid was observed in the D₂O formulation by week 8. At 60° C. storage condition (FIG. 11C),

animals Animal behavior is recorded at predetermined time intervals to evaluate the acceptance of the ophthalmic formulations

Example 16—In Vivo Rabbit Eye Irritation Test

The exemplary compositions disclosed herein are subjected to rabbit eye irritation test to evaluate their safety profile. The test composition are tested for eye irritation test in New Zealand Rabbits (see for example Abraham M H, et

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al., *Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis*. Toxicol Sci. 2003 December; 76(2):384-91. Epub 2003 Sep. 26; see also Gettings S D et al., *A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations*. Food Chem Toxicol. 1998 March; 36(3):209-31). The study involves single ocular administration into the right eye and the same volume of its placebo in the left eye of each of the three rabbits. Rabbits are examined immediately and after instillation of the compositions for 4, 24, 48 and 72 hours post instillation to note the signs/symptoms of eye irritation, if any. The test compositions show no sign of irritancy in cornea, iris and conjunctivae of the rabbit eyes.

Example 17—In Vivo Testing of Ophthalmic Aqueous Formulation in Guinea Pigs

Focus deprivation myopia (FDM) is achieved using a latex shield to cover one eye. For defocus-induced myopia, a latex-made facemask was held in place by a rubber-band around the head of animals, leaving both eyes, the nose, mouth and ears freely exposed. A -4.00 D lens is glued onto a plastic lens frame. The lens frame is then attached to the facemask around one eye by a fabric hook-and-loop fastener after the optical center of the lens was aligned with the pupil center. The lens is detached and cleaned on both sides with a water-wetted gauze at least once daily followed by re-attachment to the facemask. All the animals are maintained on a cycle of 12-h illumination (500 Lux) and 12-h darkness during the experimental period.

A cohort of guinea pigs at age of 3 weeks are randomly assigned to FDM (a facemask worn monocularly) or defocus-induced myopia (a -4.00 D lens worn monocularly) and control groups. The FDM groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or FDM-only. The defocus-induced myopia groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or defocus-only. The control groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or no treatment. Ocular biometric parameters are measured in both eyes of individual animals before and at 11 days of treatment.

Biometric parameters (e.g. refraction, corneal curvature, and axial components of the eye) are measured by an optometrist, orthoptist, or ophthalmologist with help from an animal care assistant during the light cycle (daytime) after removal of the facemask or lens. The optometrist, orthoptist, or ophthalmologist is masked in regard to the treatment conditions for each animal.

Refraction is measured by retinoscopy after the pupil is completely dilated by topical administration of 1% cyclopentolate hydrochloride. The results of retinoscopy are recorded as the mean value of the horizontal and vertical meridians.

Corneal curvature is measured with a keratometer modified by attachment of an +8 D lens onto the anterior surface of the keratometer. A group of stainless steel balls with diameters from 5.5 to 11.0 mm are measured by the modified keratometer. Three readings are recorded for each measurement to provide a mean result. The radius of corneal curvature is then deduced from the readings on the balls with known radii.

A-scan ultrasonograph is used to measure axial components of the eye (lens thickness and vitreous length and axial length). The conducting velocity was 1,723.3 m/s for mea-

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surement of the lens thickness and 1,540 m/s for measurement of the vitreous length as described previously. Each of the axial components is calculated as the mean of 10 repeated measurements.

Example 18—Safety and Efficacy Studies of Ophthalmic Aqueous Formulation

A clinical trial is performed to investigate the efficacy and safety of ophthalmic aqueous formulations described herein in patents with myopia. In some instances, the study is open-label, single blind, or double blind study. Patient selection criteria include myopic refraction of at least 1.0D in both eyes, and additional factors such as astigmatism, a documented myopic progression, age, sex, and/or health conditions.

The patients are randomized to receive 0.05%, 0.01%, or 0.001 atropine aqueous formulation formulated in either H₂O or deuterated water (e.g., D₂O) once nightly in both eyes. Allocation ratio in some instances is defined based the patient population.

The patients are evaluated on day 0 (baseline), day 14, day 30, and then at 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, and 36 months. At each visit, best-corrected distance log Mar visual acuity (BCVA) is assessed by an optometrist, orthoptist, or ophthalmologist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity is assessed using best-corrected distance spectacle correction with a reduced log Mar reading chart placed at 40 cm under well-lit conditions. The near point of accommodation (NPA) is measured using a RAF rule using best-corrected distance spectacle correction. Patients are instructed to move the target inwards till the N5 print becomes slightly blurred and then outwards till it just becomes clear. Accommodation amplitude is calculated as the inverse of NPA. Mesopic pupil size is measured with Procyon 3000 pupillometer. Photopic pupil size is measured using the Neuroptics pupillometer.

Cycloplegic autorefraction is determined 30 minutes after 3 drops of cyclopentolate 1% are administered at 5 minutes apart using a Canon RK-F1 autorefractor. A Zeiss IOL Master, a non-contact partial coherence interferometry, is used to measure the ocular axial length.

The primary outcome is myopia progression over the time period of the study. Safety is assessed by adverse events including allergic reactions, irritation, or development of blurring of vision in one or both eyes.

Example 19—Preparation of an Ointment Formulation Containing Atropine Sulfate

Atropine sulfate is mixed with the dispersing agent (e.g., polyethyleneglycol) under heating and sonication and this mixture is further thoroughly mixed with a molten ointment base (e.g. a mixture of wool wax, white petrolatum, and liquid paraffin). The mixture is placed in a pressure vessel, and sterilized at 125° C. for 30-45 minutes and cooled to room temperature. In another embodiment, autoclaving is conducted under nitrogen. The resulting ophthalmic ointment is aseptically filled into pre-sterilized containers (e.g. tubes).

Example 20—Atropine-Mucus Penetrating Particle Composition

A 0.01% atropine-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-en-

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abling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200 nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15° C. and about 25° C.

Example 21—Atropine Sulfate-Mucus Penetrating Particle Composition

A 0.01% atropine sulfate-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200 nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also be added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15° C. and about 25° C.

According to another aspect of the disclosure, described herein is an ophthalmic composition that comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate.

In some instances, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

In some instances, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

In some instances, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

In some instances, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some instances, the storage condition has a storage temperature of one of: about 25° C., about 40° C., or about 60° C. In some cases, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some cases, the storage condition has a relative humidity of about 60% or about 75%.

In some instances, the ophthalmic composition is in the form of an aqueous solution. In some cases, the muscarinic

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antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some instances, the ophthalmic composition further comprises an osmolarity adjusting agent. In some cases, the osmolarity adjusting agent is sodium chloride.

In some instances, the ophthalmic composition further comprises a preservative. In some cases, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, poly quaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some instances, the ophthalmic composition further comprises a buffer agent. In some cases, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some instances, the ophthalmic composition further comprises a tonicity adjusting agent. In some cases, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

In some instances, the ophthalmic composition is stored in a plastic container. In some cases, the material of the plastic container comprises low-density polyethylene (LDPE).

In some instances, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some cases, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some instances, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

In some instances, the ophthalmic composition further comprises a pH adjusting agent. In some cases, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

In some instances, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% D₂O. In some cases, the ophthalmic composition is essentially free of D₂O.

In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

In some instances, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some cases, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

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In some instances, the ophthalmic composition is not formulated as an injectable formulation.

While preferred embodiments of the present disclosure have been shown and described herein, such embodiments are provided by way of example only. Various alternatives to the embodiments described herein are optionally employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A kit comprising:
 - a. a vial comprising a pharmaceutical composition, the pharmaceutical composition comprising:
 - i. about 0.01 mg/g to about 0.5 mg/g of atropine or atropine sulfate;
 - ii. water; and
 - iii. a buffer; and
 - b. instructions for use.
2. The kit of claim 1, wherein the atropine or atropine sulfate is present in the pharmaceutical composition at a concentration of from about 0.01 mg/g to about 0.3 mg/g or from about 0.1 mg/g to about 0.2 mg/g.
3. The kit of claim 1, wherein the atropine or atropine sulfate is present in the pharmaceutical composition at a concentration of about 0.1 mg/g, about 0.2 mg/g, about 0.25 mg/g, about 0.3 mg/g, about 0.4 mg/g, or about 0.5 mg/g.
4. The kit of claim 1, wherein the buffer comprises a borate, a borate-polyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof.
5. The kit of claim 1, wherein the buffer comprises sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof.
6. The kit of claim 1, wherein the pharmaceutical composition further comprises a tonicity adjusting agent.
7. The kit of claim 6, wherein the tonicity adjusting agent comprises a halide salt of a monovalent cation.
8. The kit of claim 1, wherein the pharmaceutical composition further comprises a viscosity agent.

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9. The kit of claim 8, wherein the viscosity agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, or hydroxypropylmethyl-cellulose (HPMC).

10. The kit of claim 1, wherein the pharmaceutical composition is substantially free of a preservative.

11. The kit of claim 1, wherein the pharmaceutical composition comprises less than about 1% of a preservative.

12. The kit of claim 1, wherein the pharmaceutical composition further comprises a preservative.

13. The kit of claim 12, wherein a concentration of the preservative is from about 0.0001% to about 1%.

14. The kit of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

15. The kit of claim 1, wherein the pharmaceutical composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

16. The kit of claim 1, wherein the pharmaceutical composition has an acidic pH.

17. The kit of claim 1, wherein the pharmaceutical composition has a pH of from about 3.8 to about 6.4.

18. The kit of claim 1, wherein the pharmaceutical composition has a pH of less than 5.

19. The kit of claim 1, wherein the pharmaceutical composition is a solution.

20. The kit of claim 1, wherein the pharmaceutical composition is sterile.

21. The kit of claim 1, wherein the pharmaceutical composition further comprises a stabilizing agent.

22. The kit of claim 21, wherein the stabilizing agent is selected from the group consisting of glycerol, methionine, monothioglycerol, ethylenediaminetetraacetic acid (EDTA), ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate, magnesium, zinc and combinations thereof.

23. The kit of claim 22, wherein the stabilizing agent is EDTA.

* * * * *

(12) **United States Patent**
Ostrow et al.

(10) **Patent No.:** **US 10,888,557 B2**
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- (54) **OPHTHALMIC COMPOSITION**
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- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
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(58) **Field of Classification Search**
USPC 514/304
See application file for complete search history.

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(57) **ABSTRACT**

Provided herein is an ophthalmic composition. In some embodiments, the ophthalmic composition includes a low concentration of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. Further disclosed herein include an ophthalmic composition including a low concentration of an ophthalmic agent and deuterated water. Also disclosed herein are methods of arresting or preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described herein.

23 Claims, 13 Drawing Sheets

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Fig. 1A

		Weeks					
	Temp (°C)	0	1	1.571429	2.142857	3.428571	6.571429
T1	25	0.08			0.88		2.81
T2	40	0.08		3.47		4.48	

Fig. 1B

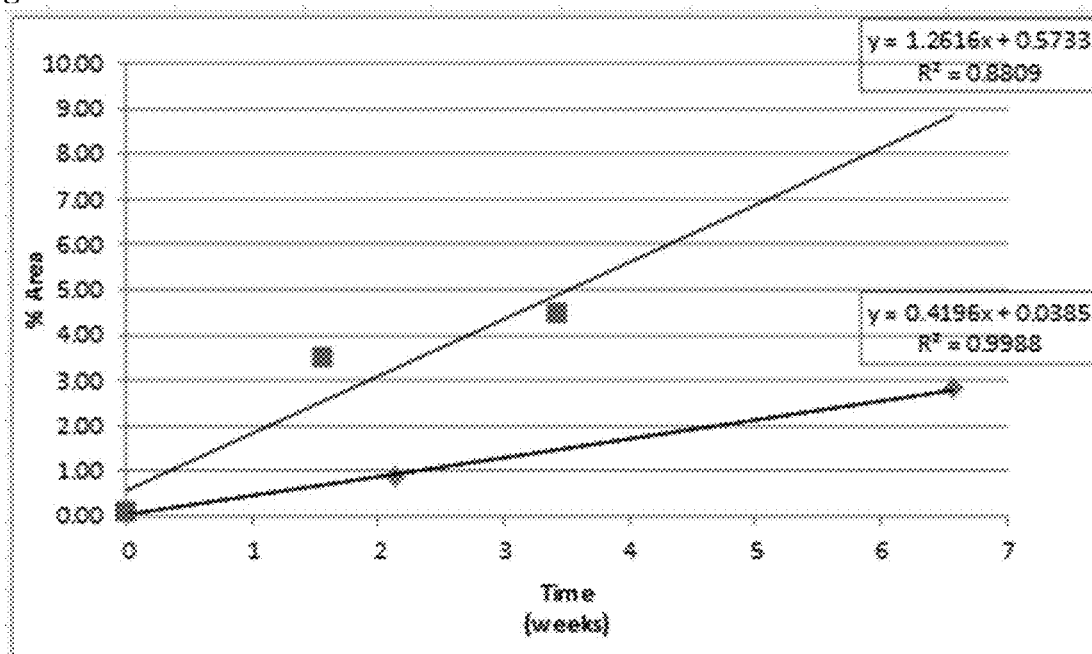


Fig. 1C

Formulation:		Average of Analysts	
Stability Prediction:		RRT 0.87	
	spec limit:	0.50	% (not more than)
			shelf life
			weeks months
rate	1.24844 at 40C	0.4	0.1
rate	0.60617 at 30C	0.8	0.2
rate	0.41477 at 25C	1.2	0.3
rate	0.07932 at 2-8C	6.3	1.6
rate	0.00694 at -20C	N/A	N/A

Fig. 2A

Weeks						
	Temp (°C)	0	1	2.142857	4	6.571429
T1	25	0.08		0.9		2.8
T2	60	0.08	10.5		11.3	

Fig. 2B

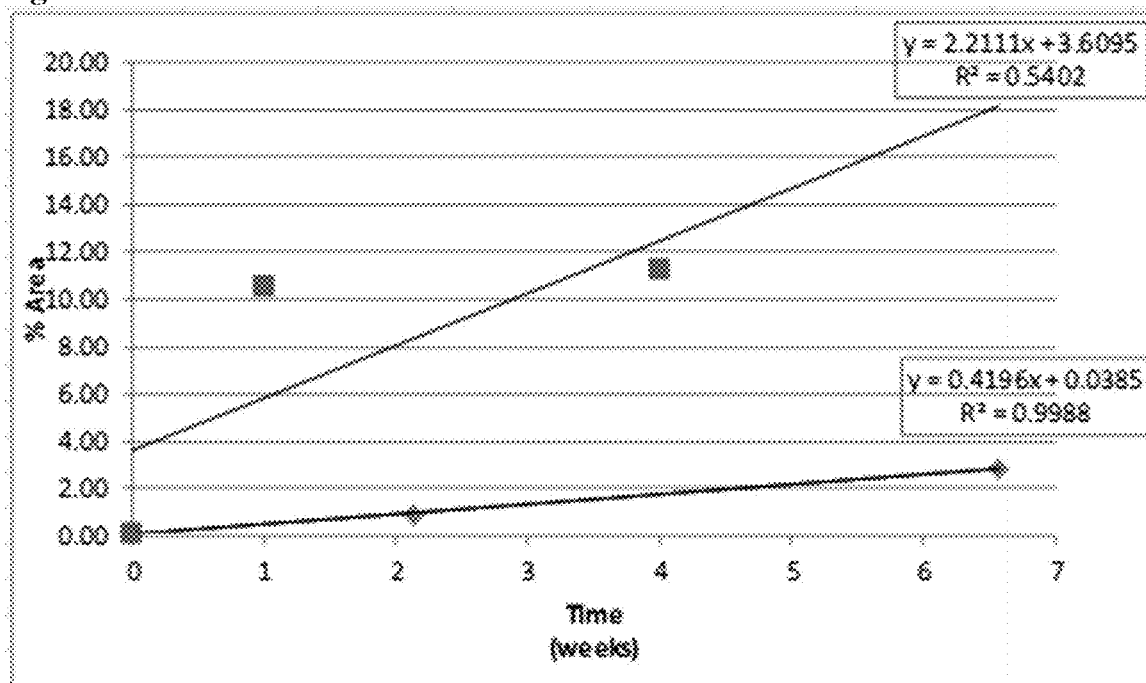


Fig. 2C

Formulation:		Average of Analysts	
Stability Prediction:		RRT 0.87	
	spec limit:	0.50	% (not more than)
			shelf life
		weeks	months
rate	0.88876 at 40C	0.6	0.1
rate	0.54051 at 30C	0.9	0.2
rate	0.41627 at 25C	1.2	0.3
rate	0.13331 at 2-8C	3.8	0.9
rate	0.02493 at -20C	N/A	N/A

Fig. 3

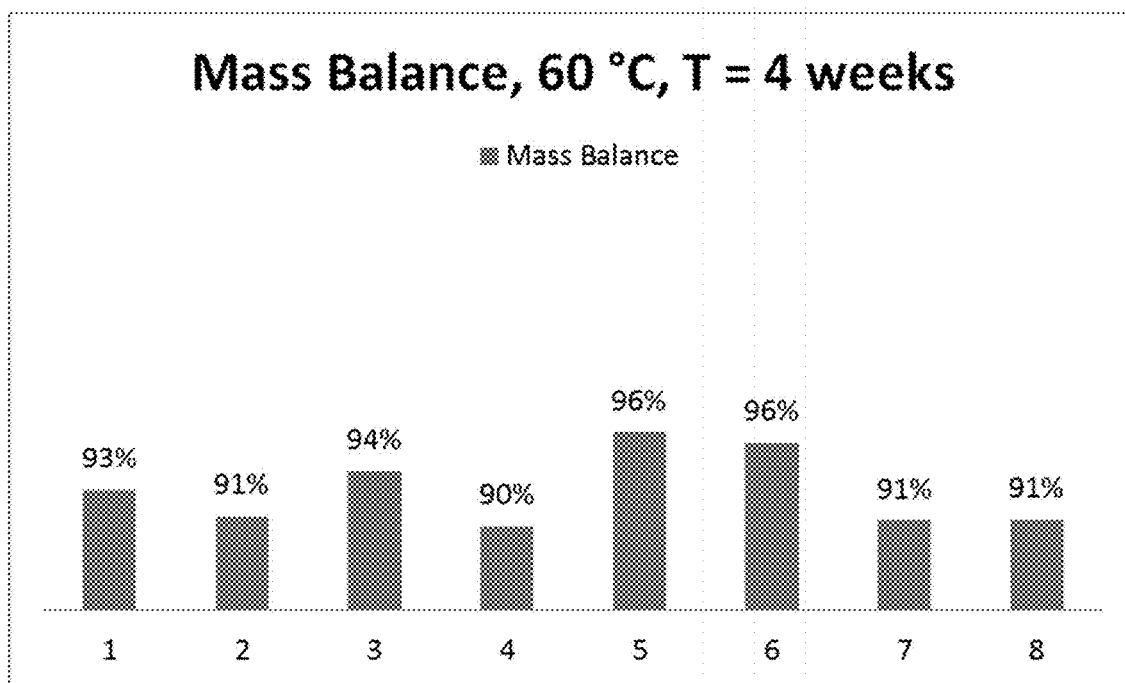


Fig. 4

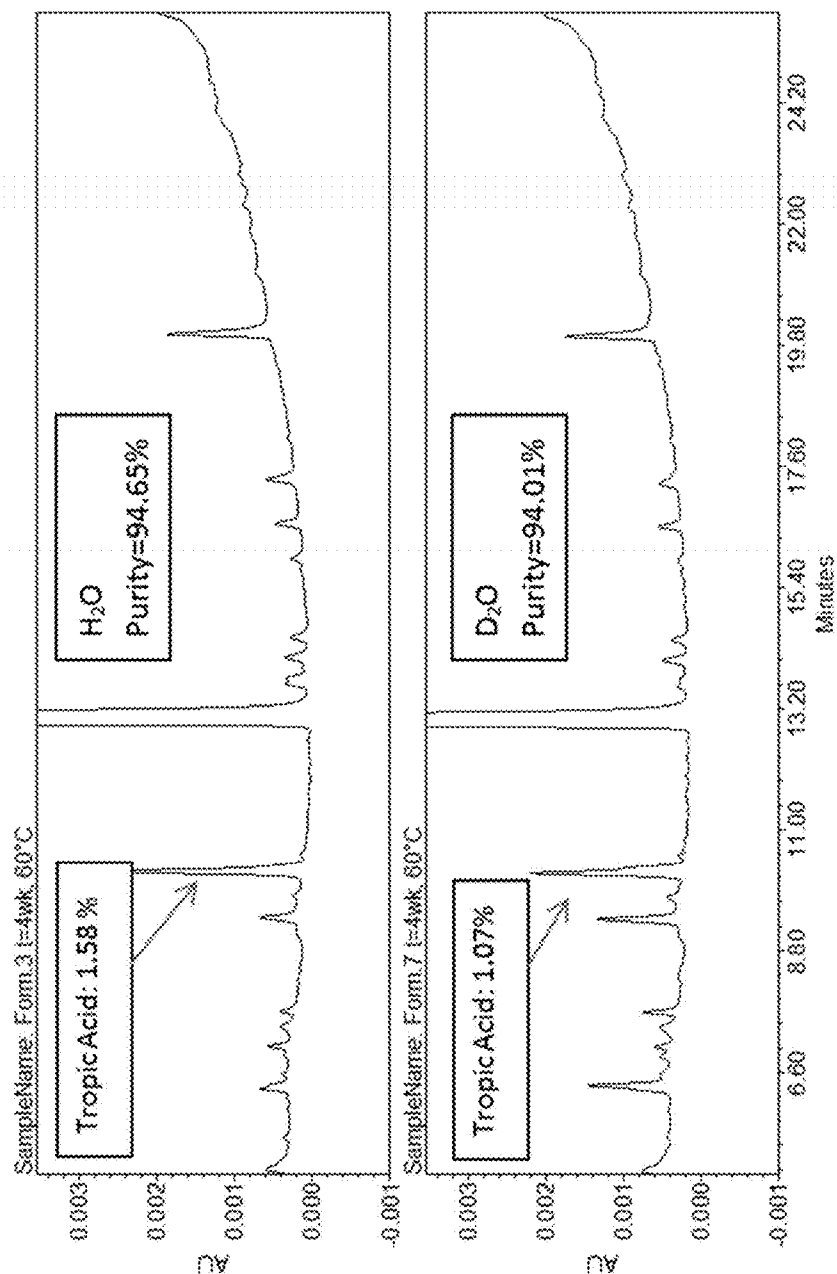


Fig. 5

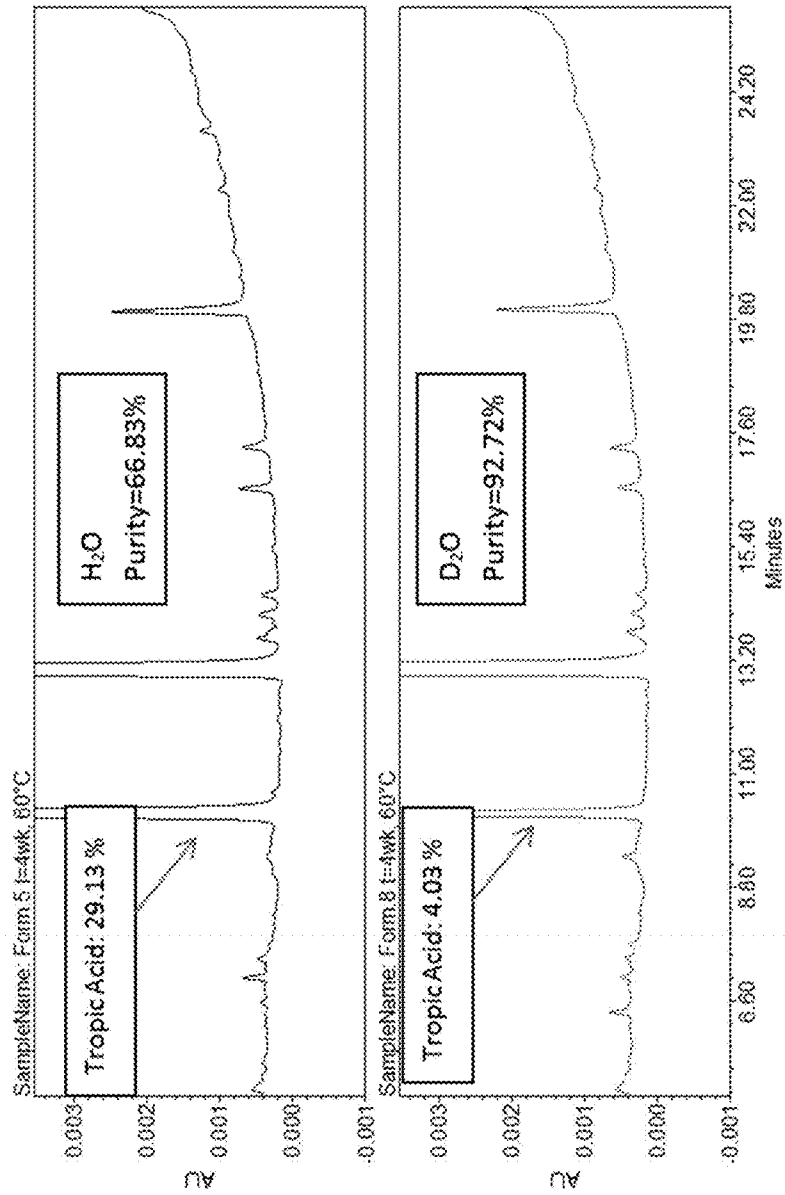


Fig. 6

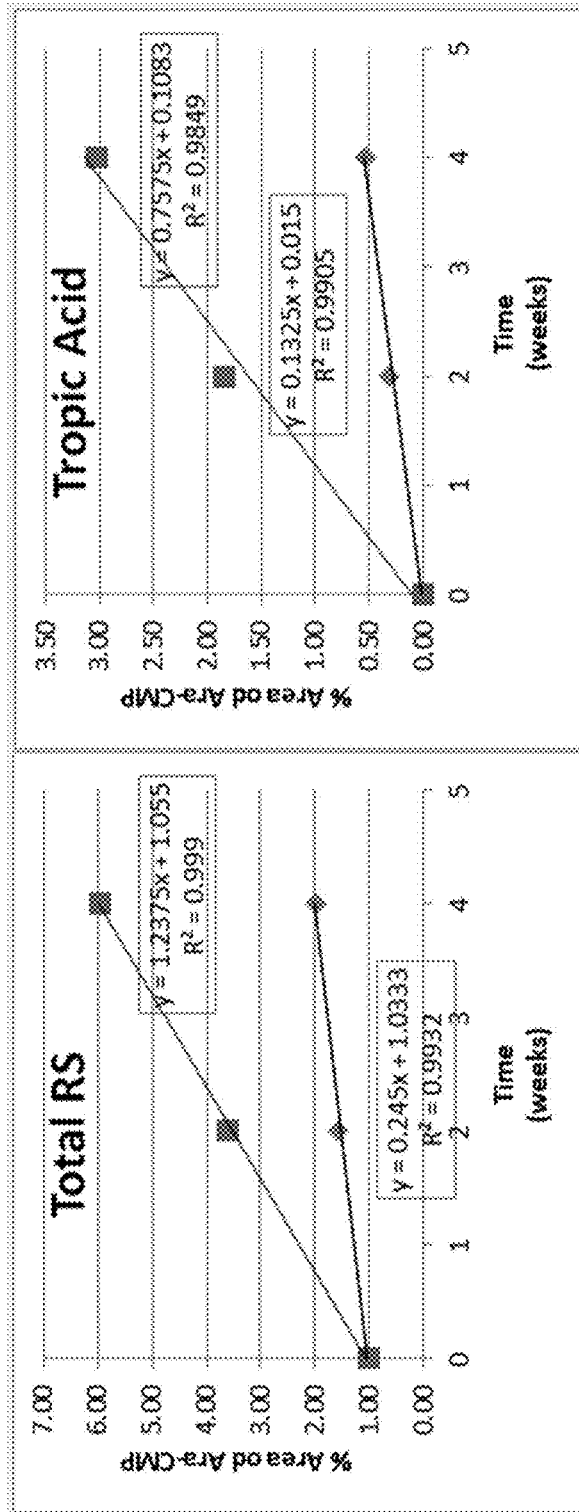


Fig. 7

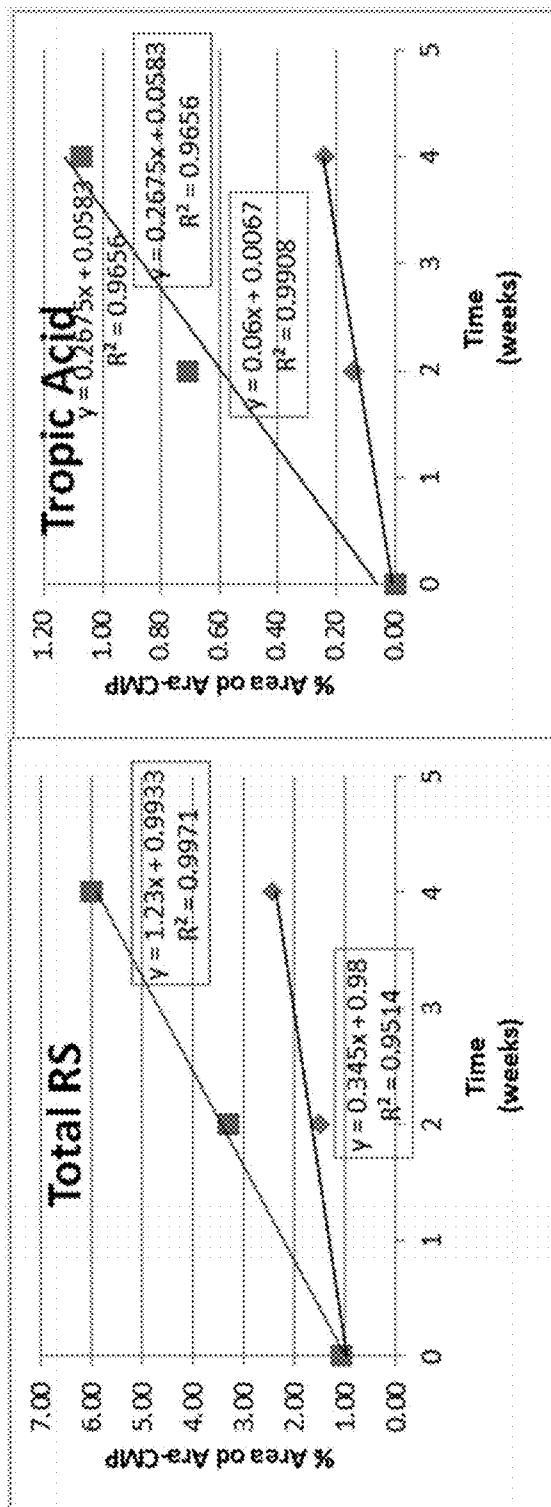


Fig. 8

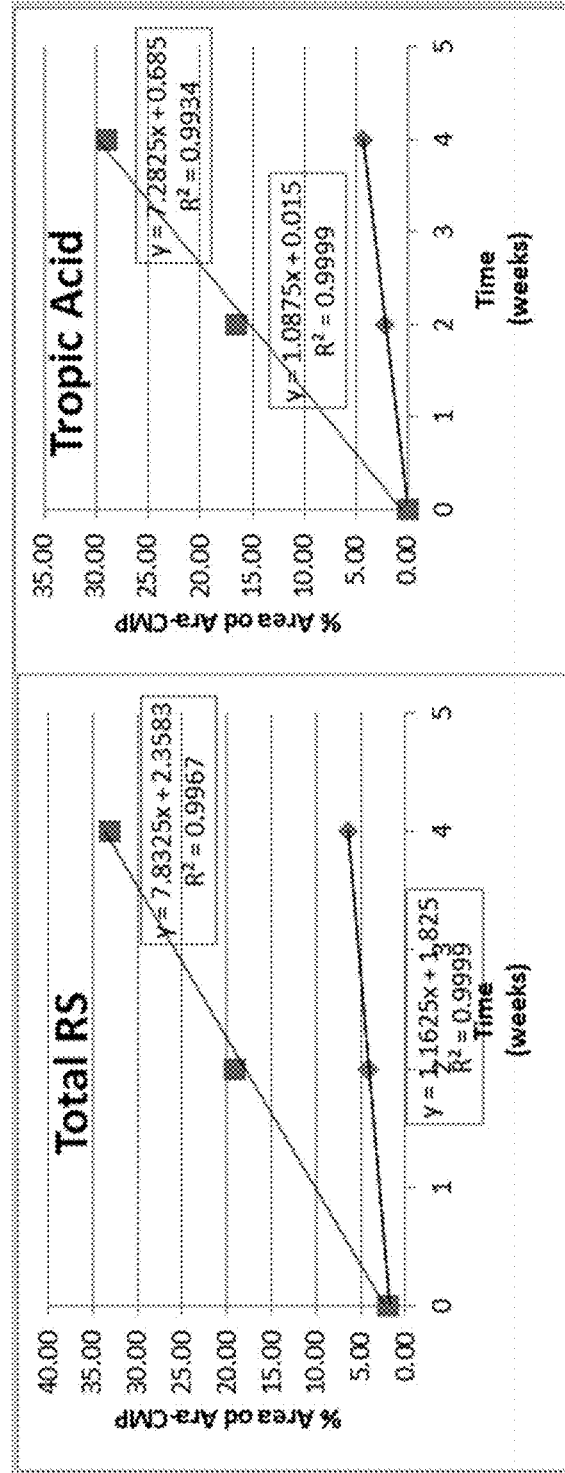


Fig. 9

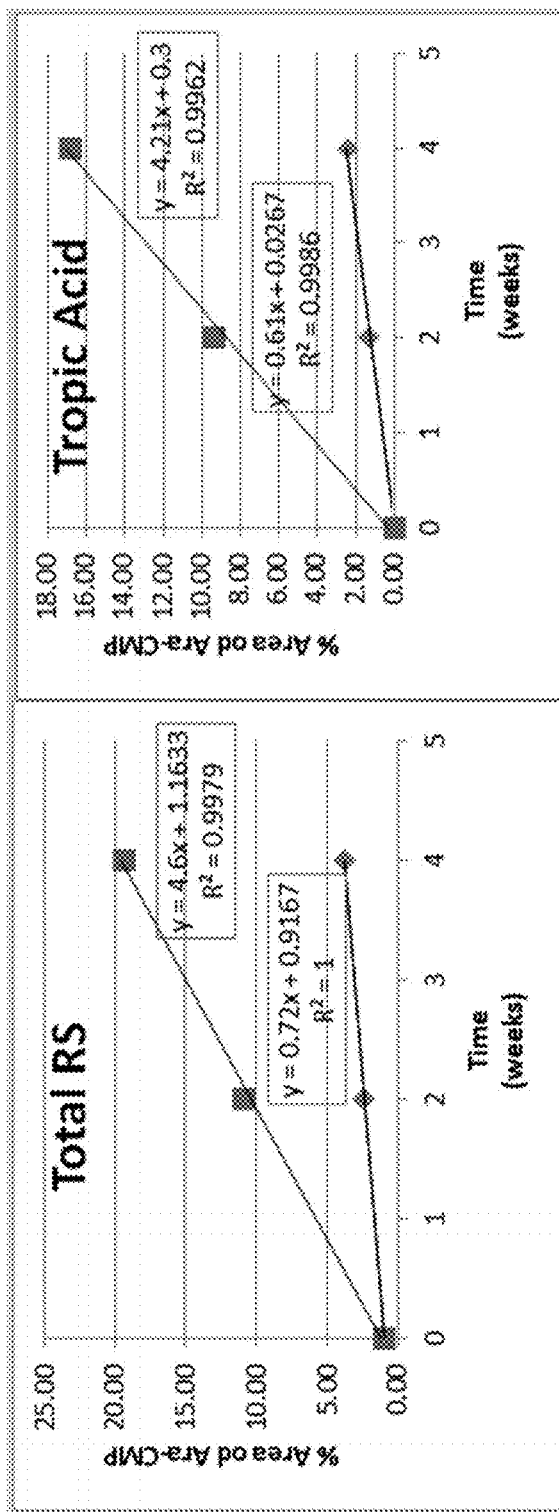


Fig. 10

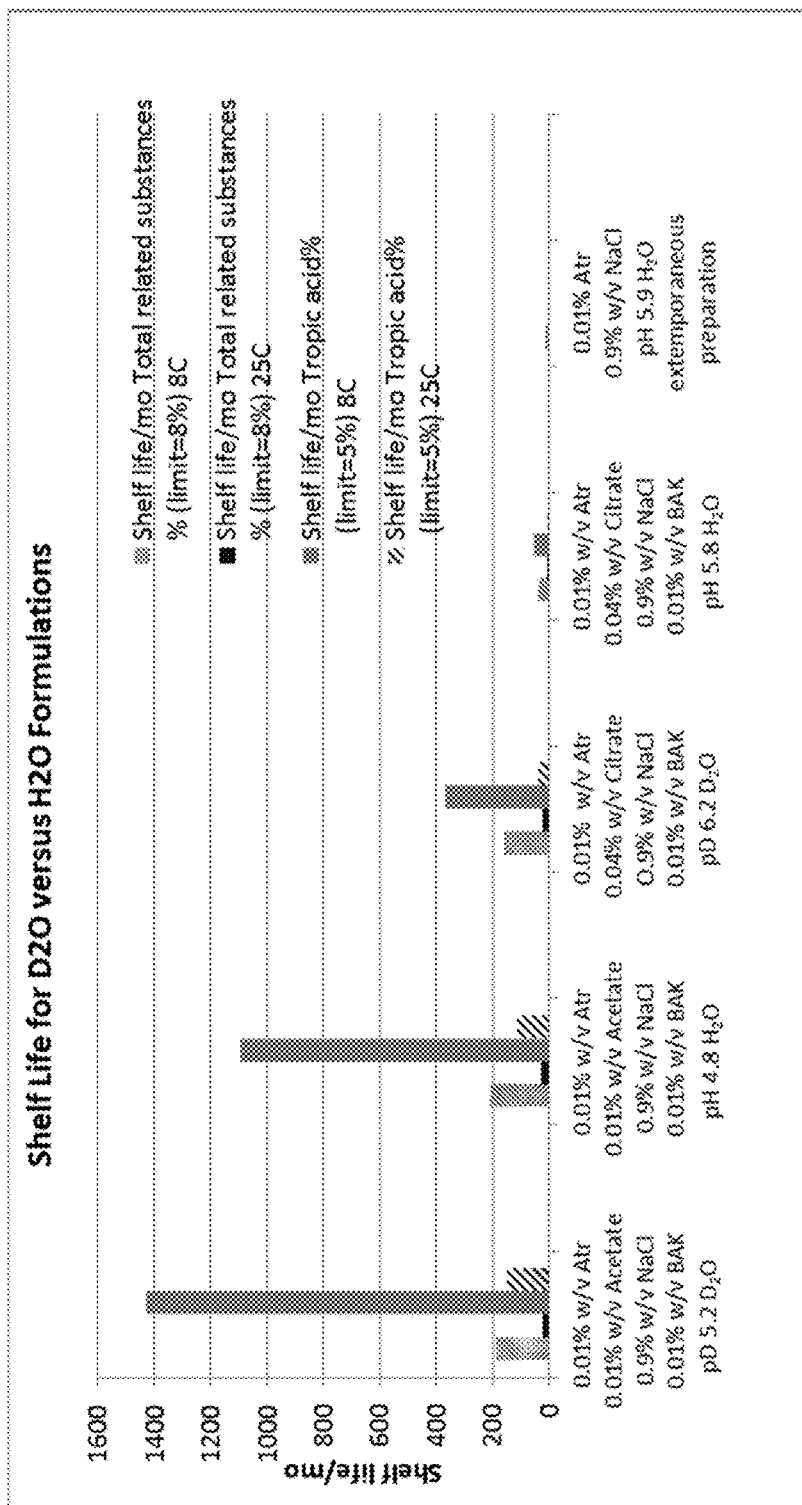


Fig. 11A

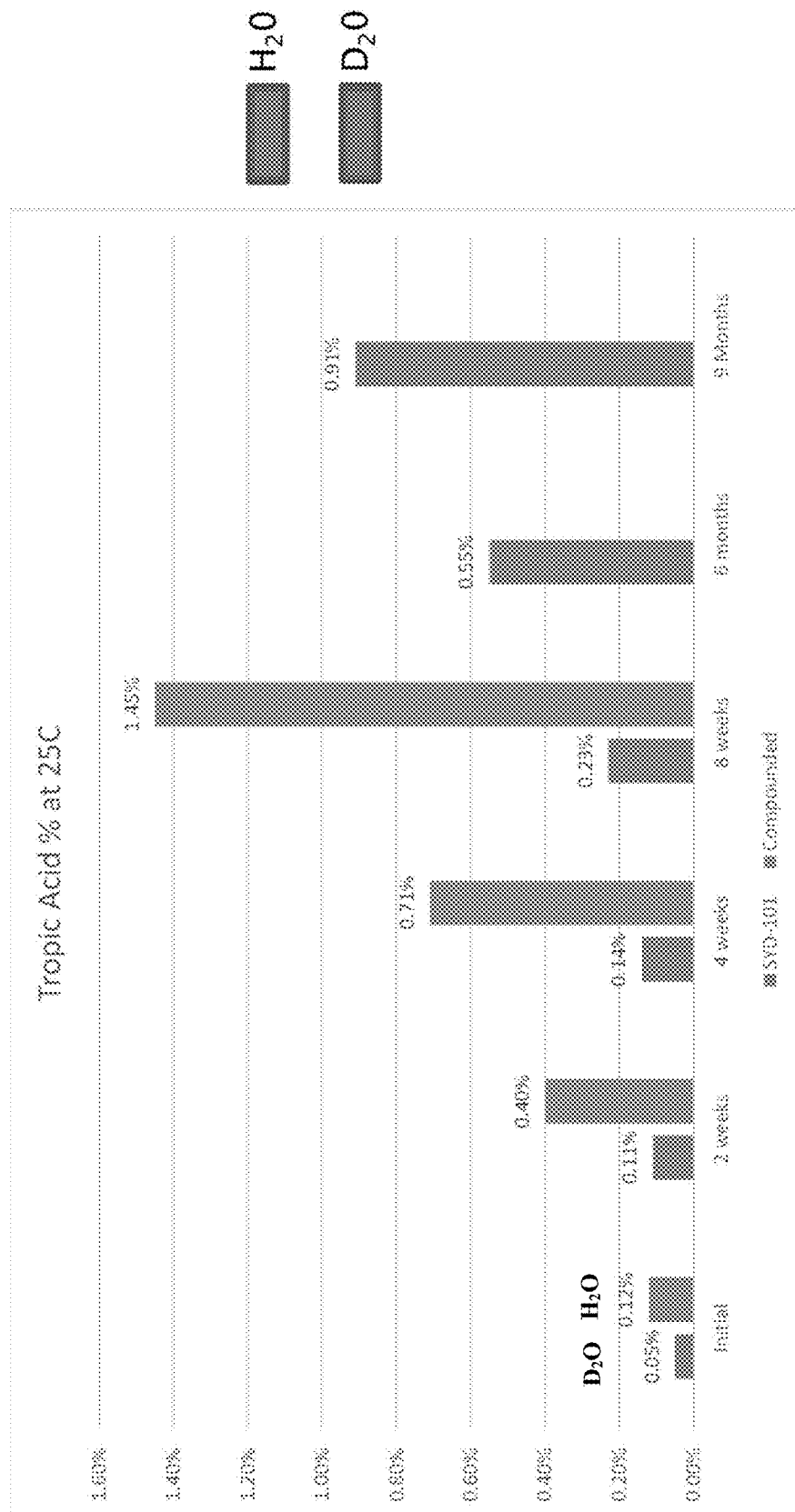


Fig. 11B

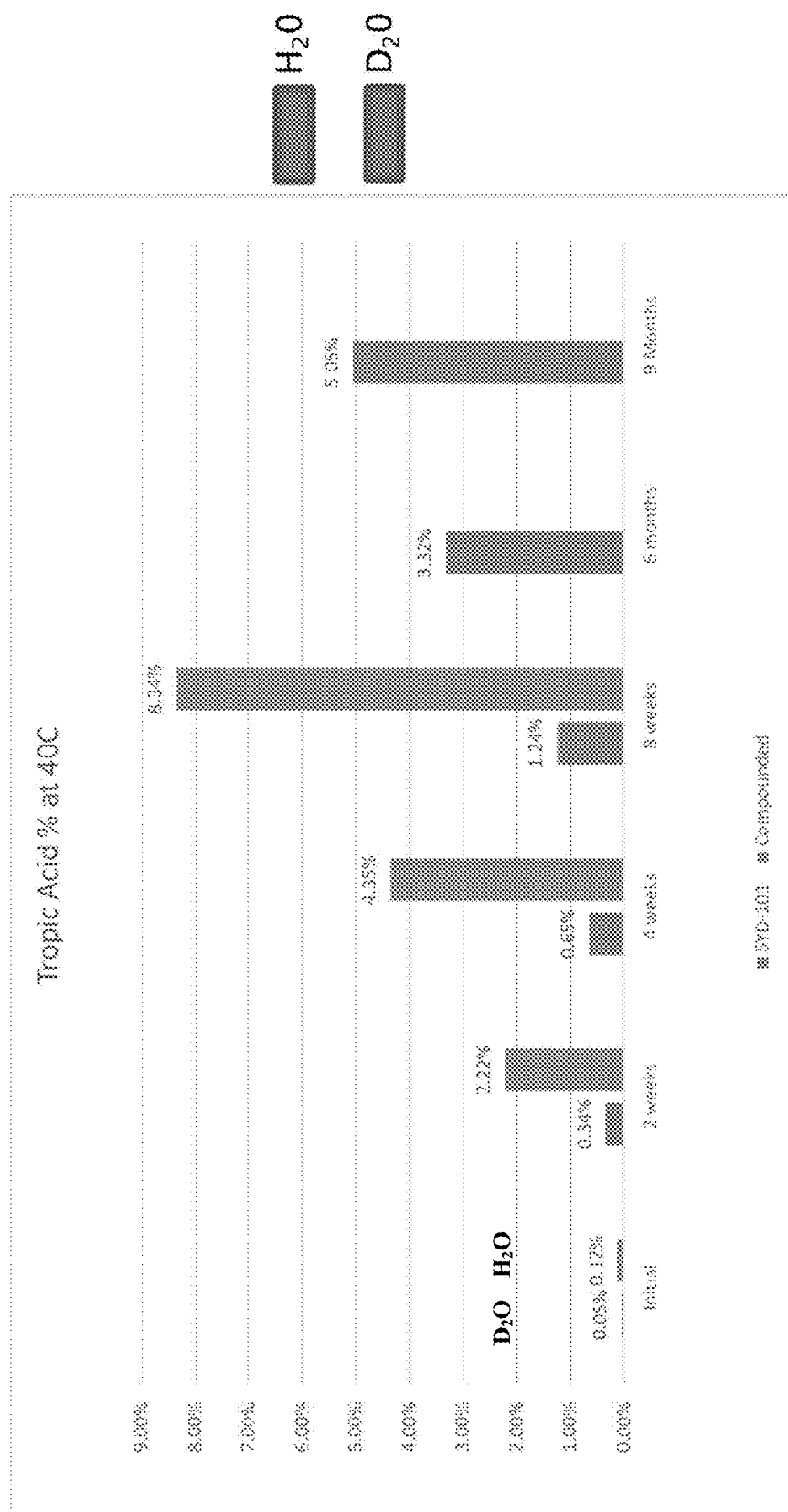
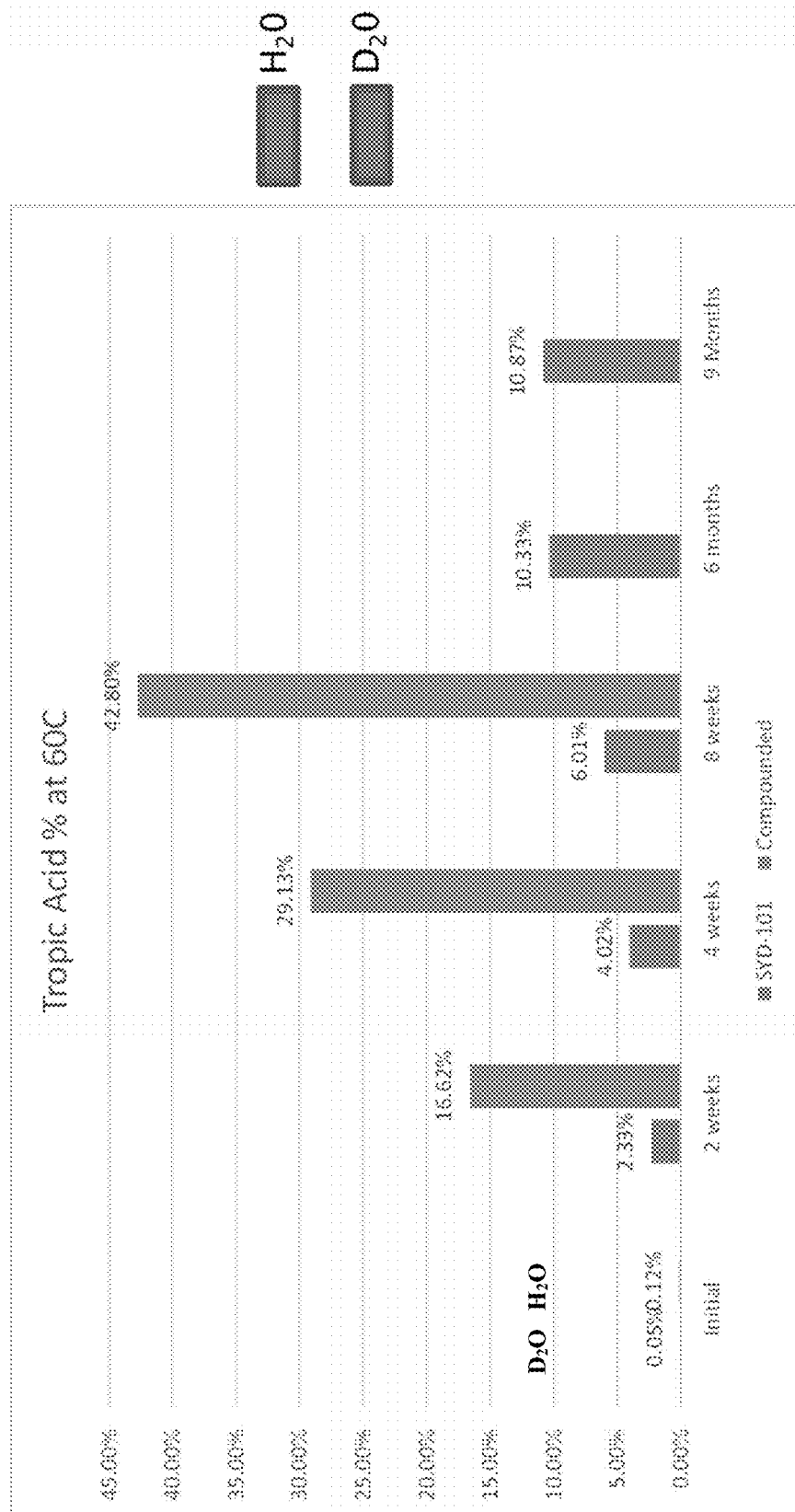


Fig. 11C



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OPHTHALMIC COMPOSITION**CROSS-REFERENCE**

This application is a continuation of U.S. application Ser. No. 16/677,538, filed Nov. 7, 2019, which is a continuation of U.S. application Ser. No. 15/568,381, filed Oct. 20, 2017, which is a § 371 U.S. National Stage Application of International Application No. PCT/US2016/029222, filed Apr. 25, 2016, which is a continuation in part of International Application No. PCT/US2015/037249, filed Jun. 23, 2015, which is a continuation in part of U.S. application Ser. No. 14/726,139, filed May 29, 2015, now U.S. Pat. No. 9,421,199, issued Aug. 23, 2016, which claims the benefit of U.S. Provisional Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2015/037249 claims the benefit of U.S. Provisional Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2016/029222 claims benefit of U.S. Provisional Application No. 62/151,926, filed Apr. 23, 2015; PCT/US2016/029222 is a continuation in part of U.S. application Ser. No. 14/726,139, filed May 29, 2015, now U.S. Pat. No. 9,421,199, issued Jun. 23, 2016 all of which their entire contents are fully incorporated herein by reference.

BACKGROUND OF THE DISCLOSURE

Pharmaceutical formulations have an expiration date which is based on the degradation of the active ingredient.

SUMMARY OF THE DISCLOSURE

Provided herein are ophthalmic compositions. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.

In some embodiments, provided herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist does not extend singlet oxygen lifetime.

In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the muscarinic antagonist quenches photogenerated singlet oxygen species in the composition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less

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than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.

In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.8, less than about 7.7, less than about 7.6, less than about 7.5, less than about 7.4, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.9, less than about 6.8, less than about 6.7, less than about 6.6, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6.

In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. As described in this disclosure, the percentage of the ophthalmic agent in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. As described in this disclosure, the potency of the ophthalmic agent in the composition after storage is based on the potency of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some embodiments, the storage condition has a storage temperature of about 25° C. In some embodiments, the storage condition has a storage temperature of about 40° C. In some embodiments, the storage condition has a storage temperature of about 60° C.

In some embodiments, the storage condition has a relative humidity of about 60%. In some embodiments, the storage condition has a relative humidity of about 75%.

In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period

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of time under storage condition. In some embodiments, the composition comprises less than 2.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid. As described in this disclosure, the percentage of the primary degradant in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

In some embodiments, the composition is in a form of an aqueous solution.

In some embodiments, the composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some embodiments, the composition is stored in a plastic container. In some embodiments, the material of the

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plastic container comprises low-density polyethylene (LDPE). In some cases, the material of the plastic container comprises polypropylene.

In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

In some embodiments, the composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, NaOD, CD_3COOD , or $\text{C}_6\text{D}_8\text{O}_7$.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the ophthalmically acceptable carrier further comprises at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

In some embodiments, the ophthalmic composition comprises one of: less than 60% of H_2O , less than 55% of H_2O , less than 50% of H_2O , less than 45% of H_2O , less than 40% of H_2O , less than 35% of H_2O , less than 30% of H_2O , less than 25% of H_2O , less than 20% of H_2O , less than 15% of H_2O ; or less than 10% of H_2O .

In some embodiments, the ophthalmic composition comprises one of: less than 5% of H_2O , less than 4% of H_2O , less than 3% of H_2O , less than 2% of H_2O , less than 1% of H_2O , less than 0.5% of H_2O , less than 0.1% of H_2O , or 0% of H_2O .

In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use.

In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

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In some embodiments, the ophthalmic composition does not comprise water-hydrolyzable derivatives of α -amino or α -hydroxy-carboxylic acids.

In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.

In some embodiments, the ophthalmic composition is a solution.

In some embodiments, disclosed herein is a method of treating an ophthalmic disorder comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of treating an ophthalmic disorder, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, disclosed herein is a method of arresting myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. Also described herein is a method of preventing myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of arresting or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years,

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or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.

In some embodiments, disclosed herein is an ophthalmic solution that comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic solution has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the ophthalmic solution comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O. In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years. In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %. In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

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In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or atropine sulfate.

In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

In some embodiments, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some embodiments, the storage condition has a storage temperature of one of: about 25° C., about 40° C., or about 60° C. In some embodiments, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C.

In some embodiments, the storage condition has a relative humidity of about 60% or about 75%.

In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate,

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potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some embodiments, the ophthalmic composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE).

In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some embodiments, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

In some embodiments, the ophthalmic composition comprises one of: less than 60% of D₂O, less than 55% of D₂O, less than 50% of D₂O, less than 45% of D₂O, less than 40% of D₂O, less than 35% of D₂O, less than 30% of D₂O, less than 25% of D₂O, less than 20% of D₂O, less than 15% of D₂O, or less than 10% of D₂O.

In some embodiments, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% of D₂O. In some embodiments, ophthalmic composition is essentially free of D₂O.

In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

Other features and technical effects of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

FIG. 1A-FIG. 1C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT

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0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 40° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

FIG. 2A-FIG. 2C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 60° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

FIG. 3 illustrates mass balance at 4 weeks and at 60° C. condition for atropine sulfate formulations disclosed in Example 9.

FIG. 4 illustrates atropine sulfate (0.010%) formulation stability in acetic acid. The atropine sulfate formulation is formulated with acetic acid and either with H₂O (top panel, Formulation 3) or D₂O (bottom panel, Formulation 7). Formulation 3 has a pH of 4.8 and Formulation 7 has a pD of 5.2. Both formulations are stored at 60° C. for 4 weeks prior to analysis.

FIG. 5 illustrates atropine sulfate (0.01%) formulation stability in citric acid. The atropine sulfate formulation is formulated with citric acid and either with H₂O (top panel, Formulation 5) or D₂O (bottom panel, Formulation 8). Formulation 5 has a pH of 5.8 and Formulation 8 has a pD of 6.2. Both formulations are stored at 60° C. for 4 weeks prior to analysis.

FIG. 6 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 4) at pH 5.8 in H₂O.

FIG. 7 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 7) at pD 5.2 in D₂O.

FIG. 8 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 5) at pH 5.8 in H₂O.

FIG. 9 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 6) at pH 5.8 in H₂O.

FIG. 10 illustrates estimated shelf lives for D₂O and H₂O formulations disclosed in Examples 11 and 12.

FIG. 11A-FIG. 11C illustrate stability of atropine sulfate formulation 8 in H₂O and D₂O under three storage conditions.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure recognizes that there is a need for a stabilized ophthalmic composition with extended shelf life upon storage. The present disclosure also recognizes that there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active agents. The present disclosure further recognizes that there is a need for an ophthalmic composition that provides convenient and effective delivery of a muscarinic antagonist such as atropine in the eye of a patient.

The present disclosure recognizes that muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people. The present disclosure also recognizes the effects of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) on reduction of axial elongation and myopia in visually impaired chick eyes, and on ocular growth and muscarinic cholinergic receptors in young rhesus monkeys.

In addition, the present disclosure recognizes that systemic absorption of muscarinic antagonist (e.g. atropine)

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sometimes leads to undesirable side effect, and that localized delivery of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) reduces or prevents the aforementioned systemic exposure.

Further, the present disclosure recognizes that some liquid muscarinic antagonist (e.g. atropine) compositions are formulated at a relatively lower pH range (e.g. less than 4.5) for stability of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). For some individuals, the lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye, which is prevented or alleviated by formulating muscarinic antagonist (e.g. atropine) compositions at higher pH ranges. For some individuals, the lower pH in some instances elicits a tear response which reduces the absorption of the drug in the eye and therefore the effectiveness.

Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present stability challenges that are less so in higher concentrations (e.g. 0.1-1%). Without wishing to be bound by any particular theory, it is contemplated that the some muscarinic antagonist (e.g. atropine) contributes to the stability of an ophthalmic composition, such as an aqueous solution. For example, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the pH or pD of the ophthalmic composition, such as with the muscarinic antagonist acting as a buffering agent. Furthermore, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the interaction between the muscarinic antagonist and other ingredients of the ophthalmic composition, which in turn affects the stability of the ophthalmic composition.

Finally, the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions. In some cases, the deuterated water is a weak acid as compared to H₂O, as such deuterated water comprises a lower concentration of the reactive species (e.g., —OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H₂O. In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

Myopia, axial elongation of the eye, affects a large proportion of the population. The onset of myopia is generally during the grade school years and progresses until growth of the eye is completed. The present disclosure recognizes the importance of compositions and treatments for preventing or arresting the development of myopia, especially compositions and treatments that allow convenient administration, reduce potential side effects, has suitable stability, and, or provide relatively consistent therapeutic effects.

Ophthalmic Muscarinic Antagonist Composition

Provided herein is an ophthalmic composition containing low concentrations of an ophthalmic agent. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. In some instances, the ophthalmic agent is a muscarinic antagonist.

Provided herein is an ophthalmic composition containing low concentrations of a muscarinic antagonist. In some

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embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the muscarinic antagonist is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the ophthalmic composition comprise a muscarinic antagonist selected from atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, or homatropine.

In some embodiments, the ophthalmic composition comprise two or more muscarinic antagonists in which the two or more muscarinic antagonists comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or any combination thereof.

In some embodiments, the ophthalmic composition comprises one or more muscarinic antagonist in combination with one or more sympathetic agonists. In some embodiments, the sympathetic agonist is selected from phenylephrine or hydroxyamphetamine. In some embodiments, the ophthalmic composition comprises one or more of muscarinic antagonist: atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combi-

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nation with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

Provided herein is an ophthalmic composition containing low concentrations of atropine or its pharmaceutically acceptable salts. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of atropine or its pharmaceutically acceptable salts for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

Provided herein is an ophthalmic composition containing low concentrations of atropine sulfate. In some embodiments, the ophthalmic composition includes from about 0.001 wt % to about 0.05 wt % of atropine sulfate for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

The present disclosure further recognizes that the clinical use of atropine as a therapy has been limited due to its ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation. Without wishing to be bound by any particular theory, it is contemplated that the limited use of atropine against myopia development, include its ocular side effects, is attributable to the concentration of atropine used in known ophthalmic formulations (e.g. 1 wt % or higher).

The present disclosure further recognizes the challenges present in formulation of compositions that contain low concentrations, especially very low concentrations (e.g. from about 0.001 wt % to about 0.5 wt %), of ophthalmic agents, such as muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). In particular, pharmaceutical compositions with ophthalmic agent at such low concentrations are difficult to maintain dose-to-dose uniformity in term of ophthalmic agent content and/or distribution.

In some aspects, described herein are formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water. In some aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent. In additional aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water has a lowered buffering capacity. In such instances, the lowered buffering capacity of the ophthalmic formulations or solutions when administered into the eye allows the ophthalmic formulation or solution to reach physiological pH at a faster rate than compared to an equivalent ophthalmic formulation or solution formulated in H₂O.

In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that does not have a dose-to-dose variation. In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

In other aspects, described herein include formulating the ophthalmic composition as an ophthalmic gel or an ophthalmic ointment. For example, some ophthalmic gel or an

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is at least 7 months. In some embodiments, the extended period of time is at least 8 months. In some embodiments, the extended period of time is at least 9 months. In some embodiments, the extended period of time is at least 10 months. In some embodiments, the extended period of time is at least 11 months. In some embodiments, the extended period of time is at least 12 months (i.e. 1 year). In some embodiments, the extended period of time is at least 18 months (i.e. 1.5 years). In some embodiments, the extended period of time is at least 24 months (i.e. 2 years). In some embodiments, the extended period of time is at least 36 months (i.e. 3 years). In some embodiments, the extended period of time is at least 3 years. In some embodiments, the extended period of time is at least 5 years, or more.

In some embodiments, the temperature of the storage condition is between about 20° C. and about 70° C. In some embodiments, the temperature of the storage condition is between about 25° C. and about 65° C., about 30° C. and about 60° C., about 35° C. and about 55° C., or about 40° C. and about 50° C. In some embodiments, the temperature of the storage condition is about 25° C. In some embodiments, the temperature of the storage condition is about 40° C. In some embodiments, the temperature of the storage condition is about 60° C.

In some embodiments, the relative humidity of the storage condition is between about 50% and about 80%, or between about 60% and about 75%. In some embodiments, the relative humidity of the storage condition is about 60%. In some embodiments, the relative humidity of the storage condition is about 75%.

In some embodiments, the composition comprises less than 60% of H₂O. In some embodiments, the composition comprises less than 55% of H₂O. In some embodiments, the composition comprises less than 50% of H₂O. In some embodiments, the composition comprises less than 45% of H₂O. In some embodiments, the composition comprises less than 40% of H₂O. In some embodiments, the composition comprises less than 35% of H₂O. In some embodiments, the composition comprises less than 30% of H₂O. In some embodiments, the composition comprises less than 25% of H₂O. In some embodiments, the composition comprises less than 20% of H₂O. In some embodiments, the composition comprises less than 15% of H₂O. In some embodiments, the composition comprises less than 10% of H₂O.

In some embodiments, the composition comprises from less than 5% of H₂O to 0% of H₂O. In some embodiments, the composition comprises less than 5% of H₂O. In some embodiments, the composition comprises less than 4.5% of H₂O. In some embodiments, the composition comprises less than 4% of H₂O. In some embodiments, the composition comprises less than 3.5% of H₂O. In some embodiments, the composition comprises less than 3% of H₂O. In some embodiments, the composition comprises less than 2.5% of H₂O. In some embodiments, the composition comprises less than 2% of H₂O. In some embodiments, the composition comprises less than 1.5% of H₂O. In some embodiments, the composition comprises less than 1% of H₂O. In some embodiments, the composition comprises less than 0.5% of H₂O. In some embodiments, the composition comprises less than 0.4% of H₂O. In some embodiments, the composition comprises less than 0.3% of H₂O. In some embodiments, the composition comprises less than 0.2% of H₂O. In some embodiments, the composition comprises less than 0.1% of H₂O. In some embodiments, the composition comprises 0% of H₂O.

In some embodiments, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about

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5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments, the composition has a pD of less than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4.

In some embodiments, the composition comprising deuterated water has a lowered buffering capacity than an equivalent composition comprising H₂O. As described elsewhere herein, in some embodiments, the lowered buffering capacity allows the composition comprising deuterated water to normalize to physiological pH at a faster rate than a composition comprising H₂O. In some embodiments, the lowered buffering capacity allows the composition to induce less tear reflex than an equivalent composition comprising H₂O.

In some instances, the composition comprising deuterated water stabilizes muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O

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aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid.

In some embodiments, the primary degradant is an early eluting related substance at RRT of 0.87-0.89 according to the UPLC method described herein (Table 10). In some instances, the early eluting related substance is referred to as RRT 0.87-0.89. In some embodiments, the primary degradant is RRT 0.87-0.89.

In some embodiments, the composition does not stabilize singlet oxygen upon irradiation with UV. In some cases, one or more of muscarinic antagonists described herein does not extend singlet oxygen lifetime. In some cases, one or more of muscarinic antagonists described herein is a radical scavenger, which quenches photogenerated singlet oxygen species within the composition. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, homatropine, scopolamine or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine or atropine sul-

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fate. In some instances, a composition comprising atropine or atropine sulfate does not stabilize singlet oxygen upon irradiation with UV. In some instances, a composition comprising atropine or atropine sulfate quenches photogenerated singlet oxygen species present in the composition.

Ophthalmic Muscarinic Antagonist Concentration

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.050%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate. As described herein, the ophthalmic agent includes optically pure stereoisomers, optically enriched stereoisomers, and a racemic mixture of stereoisomers. For example, some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a racemic mixture of D- and L-isomers; and some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a optically enriched in favor of the more ophthalmically active L-isomer.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.045%, between about 0.005% to about 0.045%, between about 0.010% to about 0.045%, between about 0.015% to about 0.045%, between about 0.020% to about 0.045%, between about 0.025% to about 0.045%, between about 0.030% to about 0.045%, between about 0.035% to about 0.045%, or between about 0.040% to about 0.045% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.040%, between about 0.005% to about 0.040%, between about 0.010% to about 0.040%, between about 0.015% to about 0.040%, between about 0.020% to about 0.040%, between about 0.025% to about 0.040%, between about 0.030% to about 0.040%, between about 0.035% to about 0.040% of the active ingredient, or phar-

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maceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.035%, between about 0.005% to about 0.035%, between about 0.010% to about 0.035%, between about 0.015% to about 0.035%, between about 0.020% to about 0.035%, between about 0.025% to about 0.035%, or between about 0.030% to about 0.035% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.030%, between about 0.005% to about 0.030%, between about 0.010% to about 0.030%, between about 0.015% to about 0.030%, between about 0.020% to about 0.030%, or between about 0.025% to about 0.030% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.025%, between about 0.005% to about 0.025%, between about 0.010% to about 0.025%, between about 0.015% to about 0.025%, or between about 0.020% to about 0.025% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.020%, between about 0.005% to about 0.020%, between about 0.010% to about 0.020%, or between about 0.015% to about 0.020% of the active ingredient, or pharmaceutically acceptable prodrug or salt

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thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.015%, between about 0.005% to about 0.015%, or between about 0.010% to about 0.015% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.010%, between about 0.005% to about 0.010%, or between about 0.008% to about 0.010% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

In some embodiments, the compositions described herein have a concentration of ophthalmic agent about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

Without wishing to be bound by any particular theory, it is contemplated herein that the low concentration of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate) in the disclosed ophthalmic composition provides sufficient and consistent therapeutic benefits to an individual in need thereof, while reducing or avoiding the ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation that are associated with ophthalmic formulations containing higher concentrations of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate).

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Aqueous Solution Stability

In some embodiments, the composition described herein comprises a buffer. In some embodiments, a buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof. In some embodiments, the composition described herein comprises buffer comprising deuterated water. In some embodiments, a deuterated buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof, formulated in deuterated water.

In some instances, borates include boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. In some cases, borates include boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

As used herein, the term polyol includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. In some embodiments, the polyols is linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. In some instances, examples of polyol include: sugars, sugar alcohols, sugar acids and uronic acids. In some cases, polyols include, but are not limited to: mannitol, glycerin, xylitol and sorbitol.

In some embodiments, phosphate buffering agents include phosphoric acid; alkali metal phosphates such as disodium hydrogen phosphate, sodium dihydrogen phosphate, trisodium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, and tripotassium phosphate; alkaline earth metal phosphates such as calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, monomagnesium phosphate, dimagnesium phosphate (magnesium hydrogen phosphate), and trimagnesium phosphate; ammonium phosphates such as diammonium hydrogen phosphate and ammonium dihydrogen phosphate; or a combination thereof. In some instances, the phosphate buffering agent is an anhydride. In some instances, the phosphate buffering agent is a hydrate.

In some embodiments, borate-polyol complexes include those described in U.S. Pat. No. 6,503,497. In some instances, the borate-polyol complexes comprise borates in an amount of from about 0.01 to about 2.0% w/v, and one or more polyols in an amount of from about 0.01% to about 5.0% w/v.

In some cases, citrate buffering agents include citric acid and sodium citrate.

In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

In some cases, organic buffering agents include Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), N-(2-Acetamido)iminodiacetic acid, N-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-N,N'-bis(2-ethanesulfonic acid (PIPES), N-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β -Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), cholamine chloride, 3-(N-morpholino)propanesulfonic acid (MOPS), N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid

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(BES), 2-[(2-Hydroxy-1,1-bis(hydroxymethyl)ethyl)amino]ethanesulfonic acid (TES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 3-(N,N-Bis[2-hydroxyethyl]amino)-2-hydroxypropanesulfonic acid (DIPSO), acetamidoglycine, 3-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propanyl]amino]-2-hydroxy-1-propanesulfonic acid (TAPSO), piperazine-1,4-bis (2-hydroxypropanesulphonic acid) (POPSO), 4-(2-hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate (HEPPSO), 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid (HEPPS), tricine, glycineamide, bicine or N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; and diethanolamine (DEA).

In some cases, amino acid buffering agents include taurine, aspartic acid and its salts (e.g., potassium salts, etc), E-aminocaproic acid, and the like.

In some instances, the composition described herein further comprises a tonicity adjusting agent. Tonicity adjusting agent is an agent introduced into a preparation such as an ophthalmic composition to reduce local irritation by preventing osmotic shock at the site of application. In some instances, buffer solution and/or a pD adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pD are considered as tonicity adjusting agents. In some cases, tonicity adjusting agents include various salts, such as halide salts of a monovalent cation. In some cases, tonicity adjusting agents include mannitol, sorbitol, dextrose, sucrose, urea, and glycerin. In some instances, suitable tonicity adjustors comprise sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.5% and about 2.0%. In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.7% and about 1.8%, about 0.8% and about 1.5%, or about 1% and about 1.3%. In some instances, the concentration of the tonicity adjusting agent is about 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, or 1.9%. In some cases, the percentage is a weight percentage.

In some cases, the composition described herein further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent used is an acid or a base. In some embodiments, the base is oxides, hydroxides, carbonates, bicarbonates and the likes. In some instances, the oxides are metal oxides such as calcium oxide, magnesium oxide and the likes; hydroxides are of alkali metals and alkaline earth metals such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the likes or their deuterated equivalents, and carbonates are sodium carbonate, sodium bicarbonates, potassium bicarbonates and the likes. In some instances, the acid is mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric acid and the likes or their deuterated equivalents. In some instances, the pD adjusting agent includes, but is not limited to, acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agent comprises DCl and NaOD.

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about 6.4. In some embodiments, the composition has an initial pD of about 6.3. In some embodiments, the composition has an initial pD of about 6.2. In some embodiments, the composition has an initial pD of about 6.1. In some embodiments, the composition has an initial pD of about 6. In some embodiments, the composition has an initial pD of about 5.9. In some embodiments, the composition has an initial pD of about 5.8. In some embodiments, the composition has an initial pD of about 5.7. In some embodiments, the composition has an initial pD of about 5.6. In some embodiments, the composition has an initial pD of about 5.5. In some embodiments, the composition has an initial pD of about 5.4. In some embodiments, the composition has an initial pD of about 5.3. In some embodiments, the composition has an initial pD of about 5.2. In some embodiments, the composition has an initial pD of about 5.1. In some embodiments, the composition has an initial pD of about 5. In some embodiments, the composition has an initial pD of about 4.9. In some embodiments, the composition has an initial pD of about 4.8. In some embodiments, the composition has an initial pD of about 4.7. In some embodiments, the composition has an initial pD of about 4.6. In some embodiments, the composition has an initial pD of about 4.5. In some embodiments, the composition has an initial pD of about 4.4. In some embodiments, the composition has an initial pD of about 4.3. In some embodiments, the composition has an initial pD of about 4.2. In some embodiments, the composition has an initial pD of about 4.1. In some embodiments, the composition has an initial pD of about 4.

In some embodiments, the pD of the composition described herein is associated with the stability of the composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a stable composition comprises a pD of less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than

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about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

As described elsewhere herein, in some instances, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., —OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., —OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the presence of deuterated water shifts the pKa of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quaternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

In some instances, the composition described herein further comprises a preservative. In some cases, a preservative

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is added at a concentration to a composition described herein to prevent the growth of or to destroy a microorganism introduced into the composition. In some instances, microorganisms refer to bacteria (e.g. *Proteus mirabilis*, *Serratia marcescens*), virus (e.g. Herpes simplex virus, herpes zoster virus), fungus (e.g. fungi from the genus *Fusarium*), yeast (e.g. *Candida albicans*), parasites (e.g. *Plasmodium* spp., *Gnathostoma* spp.), protozoan (e.g. *Giardia lamblia*), nematodes (e.g. *Onchocercus volvulus*), worm (e.g. *Dirofilaria immitis*), and/or amoeba (e.g. *Acanthamoeba*).

In some instances, the concentration of the preservative is between about 0.0001% and about 1%, about 0.001% and about 0.8%, about 0.004% and about 0.5%, about 0.008% and about 0.1%, and about 0.01% and about 0.08%. In some cases, the concentration of the preservatives is about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.008%, 0.009%, 0.009%, 0.01%, 0.015%, 0.02%, 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9% or 1.0%.

In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia (Alcon), polyquaternium-1, chlorobutanol, edetate disodium, and polyhexamethylene biguanide.

In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the material of the plastic container comprises high density polyethylene (HDPE), low density polyethylene (LDPE), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polypropylene (PP), polystyrene (PS), fluorine treated HDPE, post-consumer resin (PCR), K-resine (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the composition stored in a plastic container has a pD of between about 4 and about 8, about 4.5 and about 7.9, or about 4.9 and about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.8. In some embodiments, the composi-

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tion stored in a plastic container has a pD of less than about 5.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.

In some embodiments, the composition stored in a plastic container has a potency of at least 70% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 75% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 99% after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25° C., about 40° C., or about 60° C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

In some embodiments, the composition stored in a plastic container has a potency of at least 80% at a temperature of

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about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 85% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 90% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 93% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 95% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 97% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 98% at a temperature of about 25° C., about 40° C., or about 60° C. In some embodiments, the composition stored in a plastic container has a potency of at least 99% at a temperature of about 25° C., about 40° C., or about 60° C.

[illegible]

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In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the

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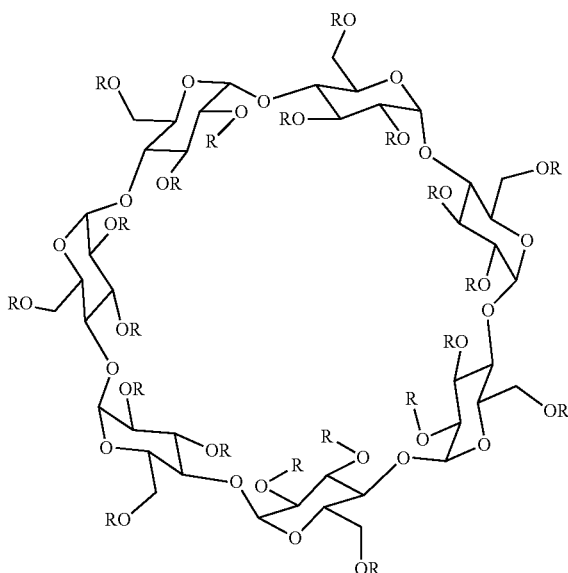
In some embodiments, the composition described herein is formulated as an aqueous solution. In some embodiments, the aqueous solution is a stable aqueous solution. In some instances, the aqueous solution is stored in a plastic container as described above. In some instances, the aqueous

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solution is not stored in a glass container. In some instances, the aqueous solution is stored in the dark. In some instances, the aqueous solution is stored in the presence of light. In some instances, the aqueous solution is stable in the presence of light.

In a specific embodiment, the ophthalmically acceptable formulations alternatively comprise a cyclodextrin. Cyclodextrins are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, referred to as α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin respectively. Cyclodextrins have a hydrophilic exterior, which enhances water-soluble, and a hydrophobic interior which forms a cavity. In an aqueous environment, hydrophobic portions of other molecules often enter the hydrophobic cavity of cyclodextrin to form inclusion compounds. Additionally, cyclodextrins are also capable of other types of nonbonding interactions with molecules that are not inside the hydrophobic cavity. Cyclodextrins have three free hydroxyl groups for each glucopyranose unit, or 18 hydroxyl groups on α -cyclodextrin, 21 hydroxyl groups on β -cyclodextrin, and 24 hydroxyl groups on γ -cyclodextrin. In some embodiments, one or more of these hydroxyl groups are reacted with any of a number of reagents to form a large variety of cyclodextrin derivatives, including hydroxypropyl ethers, sulfonates, and sulfoalkylethers. Shown below is the structure of β -cyclodextrin and the hydroxypropyl- β -cyclodextrin (HP β CD).



R = H
 β -cyclodextrin

R = $\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$
hydroxypropyl β -cyclodextrin

In some embodiments, the use of cyclodextrins in the pharmaceutical compositions described herein improves the solubility of the drug. Inclusion compounds are involved in many cases of enhanced solubility; however other interactions between cyclodextrins and insoluble compounds also improves solubility. Hydroxypropyl- β -cyclodextrin (HP β CD) is commercially available as a pyrogen free product. It is a nonhygroscopic white powder that readily dissolves in water. HP β CD is thermally stable and does not degrade at neutral pH. Thus, cyclodextrins improve the solubility of a therapeutic agent in a composition or formu-

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lation. Accordingly, in some embodiments, cyclodextrins are included to increase the solubility of the ophthalmically acceptable ophthalmic agents within the formulations described herein. In other embodiments, cyclodextrins in addition serve as controlled release excipients within the formulations described herein.

By way of example only, cyclodextrin derivatives for use include α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxyethyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, sulfated β -cyclodextrin, sulfated α -cyclodextrin, sulfobutyl ether β -cyclodextrin.

The concentration of the cyclodextrin used in the compositions and methods disclosed herein varies according to the physiochemical properties, pharmacokinetic properties, side effect or adverse events, formulation considerations, or other factors associated with the therapeutically ophthalmic agent, or a salt or prodrug thereof, or with the properties of other excipients in the composition. Thus, in certain circumstances, the concentration or amount of cyclodextrin used in accordance with the compositions and methods disclosed herein will vary, depending on the need. When used, the amount of cyclodextrins needed to increase solubility of the ophthalmic agent and/or function as a controlled release excipient in any of the formulations described herein is selected using the principles, examples, and teachings described herein.

Other stabilizers that are useful in the ophthalmically acceptable formulations disclosed herein include, for example, fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinyl pyrrolidones, polyvinyl ethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof. In some embodiments, amide analogues of stabilizers are also used. In further embodiments, the chosen stabilizer changes the hydrophobicity of the formulation, improves the mixing of various components in the formulation, controls the moisture level in the formula, or controls the mobility of the phase.

In other embodiments, stabilizers are present in sufficient amounts to inhibit the degradation of the ophthalmic agent. Examples of such stabilizing agents, include, but are not limited to: glycerol, methionine, monothioglycerol, EDTA, ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate and other heparinoids, divalent cations such as magnesium and zinc, or combinations thereof.

Additional useful stabilization agents for ophthalmically acceptable formulations include one or more anti-aggregation additives to enhance stability of ophthalmic formulations by reducing the rate of protein aggregation. The anti-aggregation additive selected depends upon the nature of the conditions to which the ophthalmic agents, for example a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), are exposed. For example, certain formulations undergoing agitation and thermal stress require a different anti-aggregation additive than a formulation undergoing lyophilization and reconstitution. Useful anti-aggregation additives include, by way of example only, urea, guanidinium chloride, simple amino acids such as glycine or arginine, sugars, polyalcohols, polysorbates, polymers such as polyethylene glycol and dextrans, alkyl saccharides, such as alkyl glycoside, and surfactants.

Other useful formulations optionally include one or more ophthalmically acceptable antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid, methionine, sodium

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thiosulfate and sodium metabisulfite. In one embodiment, antioxidants are selected from metal chelating agents, thiol containing compounds and other general stabilizing agents.

Still other useful compositions include one or more ophthalmically acceptable surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

In some embodiments, the ophthalmically acceptable pharmaceutical formulations described herein are stable with respect to compound degradation (e.g. less than 30% degradation, less than 25% degradation, less than 20% degradation, less than 15% degradation, less than 10% degradation, less than 8% degradation, less than 5% degradation, less than 3% degradation, less than 2% degradation, or less than 5% degradation) over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 3 months, at least about 4 months, at least about 5 months, or at least about 6 months under storage conditions (e.g. room temperature). In other embodiments, the formulations described herein are stable with respect to compound degradation over a period of at least about 1 week. Also described herein are formulations that are stable with respect to compound degradation over a period of at least about 1 month.

In other embodiments, an additional surfactant (co-surfactant) and/or buffering agent is combined with one or more of the pharmaceutically acceptable vehicles previously described herein so that the surfactant and/or buffering agent maintains the product at an optimal pD for stability. Suitable co-surfactants include, but are not limited to: a) natural and synthetic lipophilic agents, e.g., phospholipids, cholesterol, and cholesterol fatty acid esters and derivatives thereof; b) nonionic surfactants, which include for example, polyoxyethylene fatty alcohol esters, sorbitan fatty acid esters (Spans), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20) and other Tweens, sorbitan esters, glycerol esters, e.g., Myrj and glycerol triacetate (triacetin), polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, polysorbate 80, poloxamers, poloxamines, polyoxyethylene castor oil derivatives (e.g., Cremophor® RH40, Cremphor A25, Cremphor A20, Cremophor® EL) and other Cremophors, sulfosuccinates, alkyl sulphates (SLS); PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprates (Labrasol), PEG-4 glyceryl caprylate/caprates (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 444/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprates; Brij® 700, ascorbyl-6-palmitate, stearylamine, sodium lauryl sulfate, polyoxethyleneglycerol triiricinoleate, and any combinations or mixtures thereof; c) anionic surfactants include, but are not limited to, calcium carboxymethylcellulose, sodium carboxymethylcellulose, sodium sulfosuccinate, dioctyl, sodium alginate, alkyl polyoxyethylene sulfates, sodium lauryl sulfate, triethanolamine stearate, potassium laurate, bile salts, and any combinations or mixtures thereof;

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and d) cationic surfactants such as cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride.

In a further embodiment, when one or more co-surfactants are utilized in the ophthalmically acceptable formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and is present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%.

In one embodiment, the surfactant has an HLB value of 0 to 20. In additional embodiments, the surfactant has an HLB value of 0 to 3, of 4 to 6, of 7 to 9, of 8 to 18, of 13 to 15, of 10 to 18.

pD

In some embodiments, the pD of a composition described herein is adjusted (e.g., by use of a buffer and/or a pD adjusting agent) to an ophthalmically compatible pD range of from about 4 to about 8, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition has a pD of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6.0 to about 7.0.

In some embodiments, useful formulations include one or more pD adjusting agents or buffering agents. Suitable pD adjusting agents or buffers include, but are not limited to acetate, bicarbonate, ammonium chloride, citrate, phosphate, deuterated forms of acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agents or buffers include deuterated hydrochloric acid (DCl), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).

In one embodiment, when one or more buffers are utilized in the formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and are present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%. In certain embodiments of the present disclosure, the amount of buffer included in the gel formulations are an amount such that the pD of the gel formulation does not interfere with the body's natural buffering system.

In one embodiment, diluents are also used to stabilize compounds because they provide a more stable environment. In some instances, salts dissolved in buffered solutions (which also provides pD control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

In some embodiments, the pD is calculated according to the formula disclosed in Glasoe et al., "Use of glass electrodes to measure acidities in deuterium oxide," J. Physical Chem. 64(1): 188-190 (1960). In some embodiment, the pD is calculated as $pD = pH^* + 0.4$, in which pH* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).

In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4 and about 8, between about 4.5 and about 8, between about 4.9 and about 7.9, between about 5.4 and about 7.9, between about 5.9 and about 7.9, between about 6.4 and about 7.9, or between about 7.4 and about 7.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.5, between about 5.0 and about 7.5, between about 5.5 and about 7.5, between about 6.0 and about 7.5, or between about 7.0 and about 7.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described

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In some instances, the ophthalmic aqueous composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.1. In some

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ments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

In some embodiments, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., —OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., —OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., —OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., —OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

In some embodiments, the presence of deuterated water shifts the pK_a of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

In some embodiment, the ophthalmic gel or ointment composition described herein has a pD of about 4, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, or about 7.9.

In some embodiment, the pD of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization)) of ophthalmic formulations described herein. As used in the present disclosure, the term “aqueous composition” includes compositions that are based on D₂O.

In some embodiments, the pharmaceutical formulations described herein are stable with respect to pD over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9

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months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 18 months, at least about 24 months, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pD over a period of at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, or more.

Aqueous Solution Dose-to-Dose Uniformity

Typical ophthalmic aqueous solutions are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous solution includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous solution described herein is one drop of the aqueous solution composition from the eye drop bottle.

In some cases, described herein include ophthalmic aqueous compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake

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that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

Aqueous Solution Viscosity

In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10 to about 50,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 100 to about 40,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 500 to about 30,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 1000 to about 20,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 2000 to about 10,000 cps at about 20° C. and sheer rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 4000 to about 8000 cps at about 20° C. and sheer rate of 1 s⁻¹.

In some embodiments, the ophthalmic aqueous formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 50,000 centipoise, between about 750 and 50,000 centipoise; between about 1000 and 50,000 centipoise; between about 1000 and 40,000 centipoise; between about 2000 and 30,000 centipoise; between about 3000 and 20,000 centipoise; between about 4000 and 10,000 centipoise, or between about 5000 and 8000 centipoise.

In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an

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apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

Osmolarity

In some embodiments, a composition disclosed herein is formulated in order to not disrupt the ionic balance of the eye. In some embodiments, a composition disclosed herein has an ionic balance that is the same as or substantially the same as the eye. In some embodiments, a composition disclosed herein does not does not disrupt the ionic balance of the eye.

As used herein, “practical osmolarity/osmolality” or “deliverable osmolarity/osmolality” means the osmolarity/osmolality of a composition as determined by measuring the osmolarity/osmolality of the ophthalmic agent and all excipients except the gelling and/or the thickening agent (e.g., polyoxyethylene-polyoxypropylene copolymers, carboxymethylcellulose or the like). The practical osmolarity of a composition disclosed herein is measured by a suitable method, e.g., a freezing point depression method as described in Viegas et. al., *Int. J. Pharm.*, 1998, 160, 157-162. In some instances, the practical osmolarity of a composition disclosed herein is measured by vapor pressure osmometry (e.g., vapor pressure depression method) that allows for determination of the osmolarity of a composition at higher temperatures. In some instances, vapor pressure depression method allows for determination of the osmolarity of a composition comprising a gelling agent (e.g., a thermoreversible polymer) at a higher temperature wherein the gelling agent is in the form of a gel.

In some embodiments, the osmolarity at a target site of action (e.g., the eye) is about the same as the delivered osmolarity of a composition described herein. In some embodiments, a composition described herein has a deliverable osmolarity of about 150 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 280 mOsm/L to about 370 mOsm/L or about 250 mOsm/L to about 320 mOsm/L.

The practical osmolality of an ophthalmic composition disclosed herein is from about 100 mOsm/kg to about 1000 mOsm/kg, from about 200 mOsm/kg to about 800 mOsm/kg, from about 250 mOsm/kg to about 500 mOsm/kg, or from about 250 mOsm/kg to about 320 mOsm/kg, or from about 250 mOsm/kg to about 350 mOsm/kg or from about 280 mOsm/kg to about 320 mOsm/kg. In some embodiments, a composition described herein has a practical osmolality of about 100 mOsm/L to about 1000 mOsm/L, about 200 mOsm/L to about 800 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 250 mOsm/L to about 320 mOsm/L, or about 280 mOsm/L to about 320 mOsm/L.

In some embodiments, suitable tonicity adjusting agents include, but are not limited to any pharmaceutically acceptable sugar, salt or any combinations or mixtures thereof, such as, but not limited to dextrose, glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. In some instances, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

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In some embodiment, the ophthalmic compositions described herein include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Sterility

In some embodiments, the compositions are sterilized. Included within the embodiments disclosed herein are means and processes for sterilization of a pharmaceutical composition disclosed herein for use in humans. The goal is to provide a safe pharmaceutical product, relatively free of infection causing micro-organisms. The U. S. Food and Drug Administration has provided regulatory guidance in the publication "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing" available at: <http://www.fda.gov/cder/guidance/5882fnl.htm>, which is incorporated herein by reference in its entirety.

As used herein, sterilization means a process used to destroy or remove microorganisms that are present in a product or packaging. Any suitable method available for sterilization of objects and compositions is used. Available methods for the inactivation of microorganisms include, but are not limited to, the application of extreme heat, lethal chemicals, or gamma radiation. In some embodiments, a process for the preparation of an ophthalmic formulation comprises subjecting the formulation to a sterilization method selected from heat sterilization, chemical sterilization, radiation sterilization or filtration sterilization. The method used depends largely upon the nature of the device or composition to be sterilized. Detailed descriptions of many methods of sterilization are given in Chapter 40 of Remington: The Science and Practice of Pharmacy published by Lippincott, Williams & Wilkins, and is incorporated by reference with respect to this subject matter.

Filtration

Filtration sterilization is a method used to remove but not destroy microorganisms from solutions. Membrane filters are used to filter heat-sensitive solutions. Such filters are thin, strong, homogenous polymers of mixed cellulosic esters (MCE), polyvinylidene fluoride (PVF; also known as PVDF), or polytetrafluoroethylene (PTFE) and have pore sizes ranging from 0.1 to 0.22 μ m. Solutions of various characteristics are optionally filtered using different filter membranes. For example, PVF and PTFE membranes are well suited to filtering organic solvents while aqueous solutions are filtered through PVF or MCE membranes. Filter apparatus are available for use on many scales ranging from the single point-of-use disposable filter attached to a syringe up to commercial scale filters for use in manufacturing plants. The membrane filters are sterilized by autoclave or chemical sterilization. Validation of membrane filtration systems is performed following standardized protocols (Microbiological Evaluation of Filters for Sterilizing Liquids, Vol 4, No. 3. Washington, D.C.: Health Industry Manufacturers Association, 1981) and involve challenging the membrane filter with a known quantity (ca. $10^7/\text{cm}^2$) of unusually small microorganisms, such as *Brevundimonas diminuta* (ATCC 19146).

Pharmaceutical compositions are optionally sterilized by passing through membrane filters. Formulations comprising nanoparticles (U.S. Pat. No. 6,139,870) or multilamellar vesicles (Richard et al., International Journal of Pharmaceu-

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tics (2006), 312(1-2):144-50) are amenable to sterilization by filtration through 0.22 μ m filters without destroying their organized structure.

In some embodiments, the methods disclosed herein comprise sterilizing the formulation (or components thereof) by means of filtration sterilization. In ophthalmic gel compositions that includes thermosetting polymers, filtration is carried out below (e.g. about 5° C.) the gel temperature (Tgel) of a formulation described herein and with viscosity that allows for filtration in a reasonable time using a peristaltic pump (e.g. below a theoretical value of 100 cP).

Accordingly, provided herein are methods for sterilization of ophthalmic formulations that prevent degradation of polymeric components (e.g., thermosetting and/or other viscosity enhancing agents) and/or the ophthalmic agent during the process of sterilization. In some embodiments, degradation of the ophthalmic agent (e.g., a muscarinic antagonist such as atropine or atropine sulfate) is reduced or eliminated through the use of specific pH ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pH range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation Sterilization

One advantage of radiation sterilization is the ability to sterilize many types of products without heat degradation or other damage. The radiation commonly employed is beta radiation or alternatively, gamma radiation from a ^{60}Co source. The penetrating ability of gamma radiation allows its use in the sterilization of many product types, including solutions, compositions and heterogeneous mixtures. The germicidal effects of irradiation arise from the interaction of gamma radiation with biological macromolecules. This interaction generates charged species and free-radicals. Subsequent chemical reactions, such as rearrangements and cross-linking processes, result in the loss of normal function for these biological macromolecules. The formulations described herein are also optionally sterilized using beta irradiation.

Sterilization by Heat

Many methods are available for sterilization by the application of high heat. One method is through the use of a saturated steam autoclave. In this method, saturated steam at a temperature of at least 121° C. is allowed to contact the object to be sterilized. The transfer of heat is either directly to the microorganism, in the case of an object to be sterilized, or indirectly to the microorganism by heating the bulk of an aqueous solution to be sterilized. This method is widely practiced as it allows flexibility, safety and economy in the sterilization process.

Microorganisms

In some embodiments, the compositions are substantially free of microorganisms. Acceptable bioburden or sterility levels are based on applicable standards that define therapeutically acceptable compositions, including but not lim-

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ited to United States Pharmacopeia Chapters <111> et seq. For example, acceptable sterility (e.g., bioburden) levels include about 10 colony forming units (cfu) per gram of formulation, about 50 cfu per gram of formulation, about 100 cfu per gram of formulation, about 500 cfu per gram of formulation or about 1000 cfu per gram of formulation. In some embodiments, acceptable bioburden levels or sterility for formulations include less than 10 cfu/mL, less than 50 cfu/mL, less than 500 cfu/mL or less than 1000 cfu/mL microbial agents. In addition, acceptable bioburden levels or sterility include the exclusion of specified objectionable microbiological agents. By way of example, specified objectionable microbiological agents include but are not limited to *Escherichia coli* (*E. coli*), *Salmonella* sp., *Pseudomonas aeruginosa* (*P. aeruginosa*) and/or other specific microbial agents.

An important component of the sterility assurance quality control, quality assurance and validation process is the method of sterility testing. Sterility testing, by way of example only, is performed by two methods. The first is direct inoculation wherein a sample of the composition to be tested is added to growth medium and incubated for a period of time up to 21 days. Turbidity of the growth medium indicates contamination. Drawbacks to this method include the small sampling size of bulk materials which reduces sensitivity, and detection of microorganism growth based on a visual observation. An alternative method is membrane filtration sterility testing. In this method, a volume of product is passed through a small membrane filter paper. The filter paper is then placed into media to promote the growth of microorganisms. This method has the advantage of greater sensitivity as the entire bulk product is sampled. The commercially available Millipore Steritest sterility testing system is optionally used for determinations by membrane filtration sterility testing. For the filtration testing of creams or ointments Steritest filter system No. TLHVSL210 are used. For the filtration testing of emulsions or viscous products Steritest filter system No. TLAREM210 or TDA-REM210 are used. For the filtration testing of pre-filled syringes Steritest filter system No. TTHASY210 are used. For the filtration testing of material dispensed as an aerosol or foam Steritest filter system No. TTHVA210 are used. For the filtration testing of soluble powders in ampoules or vials Steritest filter system No. TTHADA210 or TTHADV210 are used.

Testing for *E. coli* and *Salmonella* includes the use of lactose broths incubated at 30–35° C. for 24-72 hours, incubation in MacConkey and/or EMB agars for 18-24 hours, and/or the use of Rappaport medium. Testing for the detection of *P. aeruginosa* includes the use of NAC agar. United States Pharmacopeia Chapter <62> further enumerates testing procedures for specified objectionable microorganisms.

In certain embodiments, the ophthalmic formulation described herein has less than about 60 colony forming units (CFU), less than about 50 colony forming units, less than about 40 colony forming units, or less than about 30 colony forming units of microbial agents per gram of formulation. In certain embodiments, the ophthalmic formulations described herein are formulated to be isotonic with the eye.

Endotoxins

An additional aspect of the sterilization process is the removal of by-products from the killing of microorganisms (hereinafter, "Product"). The process of depyrogenation removes pyrogens from the sample. Pyrogens are endotoxins or exotoxins which induce an immune response. An example of an endotoxin is the lipopolysaccharide (LPS)

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molecule found in the cell wall of gram-negative bacteria. While sterilization procedures such as autoclaving or treatment with ethylene oxide kill the bacteria, the LPS residue induces a proinflammatory immune response, such as septic shock. Because the molecular size of endotoxins varies widely, the presence of endotoxins is expressed in "endotoxin units" (EU). One EU is equivalent to 100 picograms of *E. coli* LPS. In some cases, humans develop a response to as little as 5 EU/kg of body weight. The bioburden (e.g., microbial limit) and/or sterility (e.g., endotoxin level) is expressed in any units as recognized in the art. In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g., <4 EU/kg of body weight of a subject) when compared to conventionally acceptable endotoxin levels (e.g., 5 EU/kg of body weight of a subject). In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of body weight of a subject. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 2 EU/kg of body weight of a subject.

In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of formulation. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of formulation. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of formulation. In some embodiments, the ophthalmic formulation has less than about 5 EU/kg Product. In other embodiments, the ophthalmic formulation has less than about 1 EU/kg Product. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/kg Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/g of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/g of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/g of unit or Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/mg of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/mg of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/mg of unit or Product. In certain embodiments, ophthalmic formulations described herein contain from about 1 to about 5 EU/mL of formulation. In certain embodiments, ophthalmic formulations described herein contain from about 2 to about 5 EU/mL of formulation, from about 3 to about 5 EU/mL of formulation, or from about 4 to about 5 EU/mL of formulation.

In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g., <0.5 EU/mL of formulation) when compared to conventionally acceptable endotoxin levels (e.g., 0.5 EU/mL of formulation). In some embodiments, the ophthalmic formulation has less than about 0.5 EU/mL of formulation. In other embodiments, the ophthalmic formulation has less than about 0.4 EU/mL of formulation. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/mL of formulation.

Pyrogen detection, by way of example only, is performed by several methods. Suitable tests for sterility include tests described in United States Pharmacopeia (USP) <71> Sterility Tests (23rd edition, 1995). The rabbit pyrogen test and the Limulus amoebocyte lysate test are both specified in the United States Pharmacopeia Chapters <85> and <151> (USP23/NF 18, Biological Tests, The United States Pharmacopeial Convention, Rockville, Md., 1995). Alternative

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pyrogen assays have been developed based upon the monocyte activation-cytokine assay. Uniform cell lines suitable for quality control applications have been developed and have demonstrated the ability to detect pyrogenicity in samples that have passed the rabbit pyrogen test and the Limulus amoebocyte lysate test (Taktak et al, J. Pharm. Pharmacol. (1990), 43:578-82). In an additional embodiment, the ophthalmic formulation is subject to depyrogenation. In a further embodiment, the process for the manufacture of the ophthalmic formulation comprises testing the formulation for pyrogenicity. In certain embodiments, the formulations described herein are substantially free of pyrogens.

Ophthalmic Muscarinic Antagonist-Mucus Penetrating Particle (MPP) Composition

Mucus-penetrating particles (MPPs) are particles that rapidly traverse mucus (e.g. human mucus). In some cases, MPPs comprise of a nanoparticle with a particle size of between about 200 nm and 500 nm. In some instances, the nanoparticle is further coated with a mucus penetrating agent. In some instances, a composition described herein is formulated with MPPs for mucus penetration. In some instances, an ophthalmic agent composition described herein is formulated with MPPs for mucus penetration. In some instances, the ophthalmic agent is a muscarinic antagonist. In some instances, a muscarinic antagonist composition described herein is formulated with MPPs for mucus penetration. In some instances, a muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine. In some instances, a muscarinic antagonist is atropine or its pharmaceutically acceptable salt thereof. In some instances, a muscarinic antagonist is atropine sulfate. In some instances, an atropine composition described herein is formulated with MPPs for mucus penetration. In some instances, an atropine sulfate composition described herein is formulated with MPPs for mucus penetration. In a non-limiting example, the MPPs for use in the disclosed composition is obtained from Kala Pharmaceuticals, Inc. (100 Beaver Street #201, Waltham, Mass. 02453).

In some embodiments, the nanoparticle comprises of any suitable material, such as an organic material, an inorganic material, a polymer, or combinations thereof. In some instances, the nanoparticle comprises of inorganic material, such as for example, a metal (e.g., Ag, Au, Pt, Fe, Cr, Co, Ni, Cu, Zn, and other transition metals), a semiconductor (e.g., silicon, silicon compounds and alloys, cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide), or an insulator (e.g., ceramics such as silicon oxide). In some instances, the nanoparticle comprises organic materials such as a synthetic polymer and/or a natural polymer. Examples of synthetic polymers include non-degradable polymers such as polymethacrylate and degradable polymers such as polylactic acid, polyglycolic acid and copolymers thereof. Examples of natural polymers include hyaluronic acid, chitosan, and collagen.

In some embodiments, the nanoparticle is coated with a mucus penetrating agent. In some instances, the mucus penetrating agent comprises any suitable material, such as a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some instances, the mucus penetrat-

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ing agent is a polymer. In some instances, the polymer a synthetic polymer (i.e., a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (e.g., a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer is a diblock copolymer, a triblock copolymer, e.g., e.g., where one block is a hydrophobic polymer and another block is a hydrophilic polymer. In some embodiments, the polymer is charged or uncharged.

Additional examples of suitable polymers include, but are not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.

In some cases, an ophthalmic agent (e.g. a muscarinic antagonist such as atropine or atropine sulfate) is present in the MPP formulation at a concentration of between about 0.001 wt % and about 0.05 wt %, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable pro-drug or salt thereof, by weight of the composition. In some

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instances, additional agents such as buffers, pH adjusting agents, and/or preservatives are formulated in the MPP formulation.

In some instances, ophthalmic agent-MPP composition is formulated using any suitable method. In some embodiments, a milling process is used to reduce the size of a solid material to form particles in the micrometer to nanometer size range. In some cases, dry and wet milling processes such as jet milling, cryo-milling, ball milling, media milling, and homogenization are known and are used in methods described herein. Generally, in a wet milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. Dry milling is a process wherein the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. In a cryo-milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients under cooled temperatures.

In some embodiments, any suitable grinding medium is used for milling. In some embodiments, a ceramic and/or polymeric material and/or a metal is used. Examples of suitable materials include zirconium oxide, silicon carbide, silicon oxide, silicon nitride, zirconium silicate, yttrium oxide, glass, alumina, alpha-alumina, aluminum oxide, polystyrene, poly(methyl methacrylate), titanium, steel. In some cases, a grinding medium has any suitable size. For example, the grinding medium has an average diameter of at least about 0.1 mm, at least about 0.2 mm, at least about 0.5 mm, at least about 0.8 mm, at least about 1 mm, at least about 2 mm, or at least about 5 mm. In some cases, the grinding medium has an average diameter of less than or equal to about 5 mm, less than or equal to about 2 mm, less than or equal to about 1 mm, less than or equal to about 0.8 mm, less than or equal to about 0.5 mm, or less than or equal to about 0.2 mm. Combinations of the above-referenced ranges are also possible (e.g., an average diameter of at least about 0.5 millimeters and less than or equal to about 1 mm). Other ranges are also possible.

In some embodiments, any suitable solvent are used for milling. In some cases, the choice of solvent is depend on factors such as the solid material (e.g., a muscarinic antagonist such as atropine) being milled, the particular type of stabilizer/mucus penetrating agent being used (e.g., one that renders the particle mucus penetrating), the grinding material to be used, among other factors. In some cases, suitable solvents are ones that do not substantially dissolve the solid material or the grinding material, but dissolve the stabilizer/mucus penetrating agent to a suitable degree. Non-limiting examples of solvents include, but are not limited to, water, buffered solutions, other aqueous solutions, alcohols (e.g., ethanol, methanol, butanol), and mixtures thereof that optionally include other components such as pharmaceutical excipients, polymers, pharmaceutical agents, salts, preservative agents, viscosity modifiers, tonicity modifier, taste masking agents, antioxidants, pH modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent is used. In some cases, a pharmaceutical agent (e.g. a muscarinic antagonist such as atropine) has any suitable solubility in these or other solvents, such as a solubility in one or more of the ranges described above for aqueous solubility or for solubility in a coating solution.

In some instances, a MPP is a MPP as described in WO2013/166385. In some instances, a MPP is a MPP as described in Lai et al., "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," PNAS 104(5):1482-1487 (2007). In some instances, an ophthalmic

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agent-MPP composition is formulated using a method as described in WO2013/166385. In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in Lai et al., "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," PNAS 104(5):1482-1487 (2007). In some instances, the ophthalmic agent is a muscarinic antagonist such as atropine or atropine sulfate.

Muscarinic Antagonist-Ophthalmic Delivery Devices and Delivery System

In some embodiments, a muscarinic antagonist described herein is delivered to a target site by an ophthalmic delivery device. In some cases, the ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist comprises atropine or atropine sulfate.

In some embodiments, an ophthalmic delivery device comprises a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device. In some instances, a non-invasive delivery device comprises topical ophthalmic drug delivery device (TODD) or a contact lens. In some instances, the ophthalmic delivery device is a biodegradable ophthalmic delivery device. In other instances, the ophthalmic delivery device is a non-biodegradable ophthalmic delivery device. In some cases, the biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In other cases, the non-biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist.

In some instances, an ophthalmic delivery device comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In some cases, the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the ophthalmic delivery device, and is configured for a controlled sustained release of the muscarinic antagonist. In some instances, the ophthalmic delivery device is a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device.

Punctal Plug

A punctal plug or tear duct plug is an ocular device that in some cases is inserted into the tear duct (or puncta) of an eye. In some instances, a punctal plug is used for the delivery of an ophthalmic composition, for example, an ophthalmic composition described herein. In some cases, a punctal plug is used for the delivery of a muscarinic antagonist formulated in deuterated water. In additional cases, a punctal plug is used for the delivery of atropine or atropine sulfate formulated in deuterated water.

In some instances, a punctal plug is used for controlled sustained release of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the period of controlled sustained release is, for example, up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 30, 45, 60 days or longer. In some instances, the period of controlled sustained release is, for example, up to 7 days. In some cases, the period of con-

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trolled sustained release is, for example, up to 14 days. In some cases, the period of controlled sustained release is, for example, up to 1 month.

In some embodiments, a punctal plug comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed within the punctal plug material, and is configured for a controlled sustained release of the muscarinic antagonist.

In some embodiments, a punctal plug described herein utilizes a diffusion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some instances, the configuration of the punctal plug is tubular with its cylindrical wall closed by transverse end walls to define a reservoir for the muscarinic antagonist (either in liquid or gel form). In some cases, at least the cylindrical wall is a membrane permeable by diffusion so that the muscarinic antagonist is released continuously at a controlled rate through the membrane into the tear fluid.

Exemplary materials for a permeable membrane for the diffusion mechanism include insoluble microporous materials of polycarbonates, polyvinyl chlorides, polyamides, copolymers of polyvinyl chloride and acrylonitrile, polysulphones, polyvinylidene fluorides, polyvinyl fluorides, polychloroethers, polyformaldehydes, acrylic resins, polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetates, polyethers, cellulose esters, porous rubbers, cross-linked poly(ethylene oxide), cross-linked polyvinyl pyrrolidone, cross-linked poly(vinyl alcohol) and polystyrenes.

In some embodiments, a punctal plug described herein utilizes an osmosis mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is tubular with domed end walls, and the device comprises a transverse impermeable elastic membrane dividing the tubular interior of the device into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. In some cases, a drug release aperture is included in the impermeable end wall of the device. When the device is placed in the aqueous environment of the eye water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

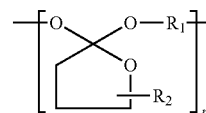
Examples of materials for an osmotic semi-permeable membrane include cellulose acetate and its derivatives, partial and completely hydrolyzed ethylene-vinyl acetate copolymers, highly plasticized polyvinyl chloride, homo- and copolymers of polyvinyl acetate, polyesters of acrylic acid and methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride; silicone polycarbonates, aromatic nitrogen-containing polymeric membranes, polymeric epoxides, copolymers of an alkylene oxide and alkyl glycidyl ether, polyurethanes, polyglycolic or polylactic acid and derivatives thereof, derivatives of polystyrene such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), ethylene-vinyl acetate copolymers.

In some embodiments, a punctal plug described herein utilizes a bioerosion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is rod-like being constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the device with tear

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fluid results in controlled sustained release of the drug by bioerosion of the matrix. In such cases, the drug is dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

Examples of bioerodible matrix materials include polyesters of the general formula —O—(W)—CO— and mixture thereof, wherein W is a lower alkylene of 1 to 7 carbons and may include a member selected from the group of alkenes of the formula $\text{—CH}_2\text{—}$, or $\text{—CH=CH}_2\text{—}$, and Y has a value such that the molecular weight of the polymer is from about 4,000 to 100,000. The polymers are polymerization-condensation products of monobasic hydroxy acid of the formula $\text{C}_n\text{H}_{2n}(\text{OH})\text{COOH}$ wherein n has a value of 1 to 7, preferably 1 or 2 and the acid is especially lactic acid or glycolic acid. Also included are copolymers derived from mixtures of these acids. Bioerodible materials also include poly(orthoesters). These materials have the following general formula:



wherein R_1 is an alkylene of 4 to 12 carbons, a cycloalkylene of 5 to 6 carbons substituted with an alkylene of 1 to 7 carbons and an alkyleneoxy of 1 to 7 carbons, and R_2 is a lower alkyl of 1 to 7 carbons.

Additional bioerodible matrix materials include: (1) Poly-anhydrides such as poly(p-carboxyphenoxy) alkyl (e.g. p-carboxyphenoxypropane) or polymeric fatty acid dimer (e.g. poly-dodecanedioic acid) compounds and further copolymers with sebacic acid, or phthalic acid such as disclosed in Chasin et al., Poly-anhydrides for Controlled Drug Delivery, *Biopharm.*, February 1988, 33-46; and Lee et al. (1988), The Use of Bioerodible Polymers and 5 fluorouracil in Glaucoma Filtration Surgery, *Invest. Ophthalmol. Vis. Sci.*, 29, 1692-1697; (2) Poly (alkyl-2-cyanoacrylates) such as poly (hexyl-2-cyanoacrylate) as described by Douglas et al. (1987), Nanoparticles in Drug Delivery, *CRC Crit. Rev. Therap. Drug Carr. System.*, 3, 233-261; and (3) Polyamino acids such as copolymers of leucine and methyl glutamate.

In some cases, a punctal plug described herein comprises a solid non-erodible rod with pores. In some instances, the release of a muscarinic antagonist takes place via diffusion through the pores. In such instances, controlled release is further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

Examples of materials for use as non-erodible rods include polymers such as hydroxyethylmethacrylate and co-polymers with methacrylic acid, methylmethacrylate, N-vinyl 2-pyrrolidone, allyl methacrylate, ethylene glycol dimethacrylate, ethylene dimethacrylate, or 1,1,1 trimethylpropane trimethacrylate, and dimethyl diphenyl methyl-vinyl polysiloxane.

In some instances, the body of the plug is wholly or partially transparent or opaque. Optionally, the body includes a tint or pigment that makes the plug easier to see when it is placed in a punctum.

In some cases, the surface of the plug body is wholly or partially coated. In some cases, the coating provides one or more of lubriciousness to aid insertion, muco-adhesiveness to improve tissue compatibility, and texture to aid in anchor-

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ing the plug within the punctum. Examples of suitable coatings include, without limitation, gelatin, collagen, hydroxyethyl methacrylate, PVP, PEG, heparin, chondroitin sulphate, hyaluronic acid, synthetic and natural proteins, and polysaccharides, thiomers, thiolated derivatives of polyacrylic acid and chitosan, polyacrylic acid, carboxymethyl cellulose and the like and combinations thereof.

In some embodiments, a punctal plug described herein is a punctal plug described in U.S. Pat. No. 5,147,647; U.S. Publication No. 2012/0277694; or 2010/0256557.

In some instances, the size of the opening of the punctal plug is from about 0.05 mm to about 2.5 mm. In some instances, it is from about 0.1 mm to about 2.0 mm, or from about 0.15 mm to about 1 mm.

In some embodiments, the amount of a muscarinic antagonist (e.g., atropine or atropine sulfate) used in the plugs depends upon the muscarinic antagonist selected, the desired doses to be delivered via the punctal plug, the desired release rate, and the melting points of the muscarinic antagonist and muscarinic antagonist-containing material.

Scleral Patch or Scleral Ring

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a scleral patch or a scleral ring. In some instances, a scleral patch or a scleral ring is a biodegradable scleral patch or scleral ring. In other instances, a scleral patch or a scleral ring is a non-biodegradable scleral patch or scleral ring. In additional instances, a scleral patch or a scleral ring is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a scleral patch comprises a multi-layered patch in which one or more layer within the patch comprises a muscarinic antagonist described herein. In some cases, a scleral ring comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the scleral patch or the scleral ring.

Cul-De Sac Inserts

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a Cul-de sac insert. In some instances, the Cul-de sac insert comprises a single-layered device comprising muscarinic antagonist dispersed within the insert material, or multilayered, solid or semisolid consistency insert. In some instances, the Cul-de sac insert is a biodegradable insert. In other instances, the Cul-de sac insert is a non-biodegradable insert. In additional instances, a Cul-de sac insert is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some instances, a Cul-de sac insert comprises a membrane-bound ocular insert, which comprises of two outer layers of a copolymer such as ethylene-vinyl acetate copolymer (EVA) and an inner layer comprising a muscarinic antagonist. In some instances, the muscarinic antagonist within the inner layer is formulated as a gel or as a solution. An exemplary membrane-bound ocular insert is Ocuserts from Alza Corp.

In some cases, a Cul-de sac insert comprises an ocular film or sheath (mucoadhesive film or sheath or collagen shields), a coil, a polymer rod, HEMA hydrogel, or polysulfone capillary fiber. In some instances, a Cul-de sac insert comprises rod-shaped water soluble insert comprising of hydroxypropyl cellulose, a muscarinic antagonist, and one or more additional excipients. In some instances, the Cul-de

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sac insert comprising a rod-shaped water soluble insert is a biodegradable insert. An example comprises Lacrisert (Merck).

Subconjunctival/Episcleral Implant

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a subconjunctival/episcleral implant. In some instances, a subconjunctival/episcleral implant is a biodegradable implant. In other instances, a subconjunctival/episcleral implant is a non-biodegradable implant. In additional instances, a subconjunctival/episcleral implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a subconjunctival/episcleral implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the subconjunctival/episcleral implant. Exemplary subconjunctival/episcleral implants include LX201 (Lux Biosciences Inc.), an episcleral implant from 3T Ophthalmics, or a subconjunctival insert from Pfizer.

Intravitreal Implants

In some embodiments, a muscarinic antagonist described herein is delivered to an eye through an intravitreal implant. In some instances, an intravitreal implant is a biodegradable implant. In other instances, an intravitreal implant is a non-biodegradable implant. In additional instances, an intravitreal implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, an intravitreal implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the intravitreal implant. Exemplary intravitreal implant comprises Durasert™ technology system (pSivida Corp.) (such as Vitrasert® and Retisert® from Bausch & Lomb Inc, and Iluvien® from Alimera sciences), Novadur™ technology system (such as Ozurdex® from Allergan), I-vation™ technology system (such as a delivery system developed from SurModics, Inc.), and NT-501 from Neurotech Pharmaceuticals.

Non-Invasive Delivery System

In some embodiments, a non-invasive delivery system comprises a topical ophthalmic agent delivery device. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device comprises a soft elastomer drug depot that floats atop the sclera under the eyelid. In some instances, the topical ophthalmic agent delivery device is a biodegradable delivery device. In other instances, the topical ophthalmic agent delivery device is a non-biodegradable delivery device. In some cases, the topical ophthalmic agent delivery device is impregnated with a muscarinic antagonist described herein. In other cases, a muscarinic antagonist is dispersed (e.g., uniformly) in the topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device is formulated for controlled sustained release of the muscarinic antagonist. In some instances, an exemplary delivery device is a topical ophthalmic drug delivery device (TODD) from Amorphex Therapeutics.

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In some embodiments, a non-invasive delivery system comprises a contact lens. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a contact lens. In some instances, the contact lens is impregnated with a muscarinic antagonist, for example, in which the muscarinic antagonist is dispersed, e.g., as colloidal structure, within the lens. In other instances, the contact lens is further combined with a muscarinic antagonist layer, and is configured for controlled sustained release to the eye. Exemplary polymers, e.g., hydrogel copolymers, for making a contact lens include at least one hydrophilic monomer and a crosslinking agent (a crosslinker being defined as a monomer having multiple polymerizable functionalities). Representative, hydrophilic monomers include: unsaturated carboxylic acids, such as methacrylic acid and acrylic acid; (meth)acrylic substituted alcohols, such as 2-hydroxyethylmethacrylate and 2-hydroxyethylacrylate; vinyl lactams, such as N-vinyl pyrrolidone; and (meth) acrylamides, such as methacrylamide and N,N-dimethylacrylamide. Typical crosslinking agents include polyvinyl, typically di- or tri-vinyl monomers, such as di- or tri(meth) acrylates of diethyleneglycol, triethyleneglycol, butyleneglycol and hexane-1,6-diol; and divinylbenzene. A specific example of a hydrogel-forming monomer mixture is polymacon, composed primarily of 2-hydroxyethylmethacrylate with a small amount of diethyleneglycol dimethacrylate as a crosslinking monomer. Optionally, the monomer mixture may include a silicone-containing monomer in order to form a silicone hydrogel copolymer. Examples of silicone-containing monomers include: monomers including a single activated unsaturated radical, such as methacryloxypropyl tris(trimethylsiloxy)silane, pentamethyldisiloxanyl methylmethacrylate, tris(trimethylsiloxy)methacryloxy propylsilane, methyl di(trimethylsiloxy)methacryloxymethyl silane, 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbamate, and 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbonate; and multifunctional ethylenically "end-capped" siloxane-containing monomers, especially difunctional monomers having two activated unsaturated radicals. A specific example of a silicone hydrogel-forming monomer mixture is balaficon, based on N-vinyl pyrrolidone and the aforementioned vinyl carbonate and carbamate monomers, disclosed in U.S. Pat. No. 5,260,000.

Ophthalmic Gel Muscarinic Antagonist Composition

Gels have been defined in various ways. For example, the United States Pharmacopoeia defines gels as semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels include a single-phase or a two-phase system. A single-phase gel consists of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Some single-phase gels are prepared from synthetic macromolecules (e.g., carbomer) or from natural gums, (e.g., tragacanth). In some embodiments, single-phase gels are generally aqueous, but will also be made using alcohols and oils. Two-phase gels consist of a network of small discrete particles.

In some embodiments, gels are also classified as being hydrophobic or hydrophilic. In certain embodiments, the base of a non-limiting example of a hydrophobic gel includes a liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, or aluminum or zinc soaps. In contrast, the base of a non-limiting example of a hydrophilic gel includes water, glycerol, or propylene glycol gelled with a suitable gelling agent (e.g., tragacanth, starch, cellulose derivatives, carboxyvinylpolymers, and magnesium-alumi-

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num silicates). In certain embodiments, the rheology of the compositions disclosed herein is pseudo plastic, plastic, thixotropic, or dilatant.

In some embodiments, the ophthalmic composition is an ophthalmic gel, and wherein the ophthalmically acceptable carrier comprises water and at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

In some embodiment, the ophthalmic gel composition described herein is a semi-solid or id in a gelled state before it is topically administered (e.g. at room temperature). For example, suitable viscosity-enhancing agents for such gels include by way of example only, gelling agents and suspending agents. In one embodiment, the enhanced viscosity formulation does not include a buffer. In other embodiments, the enhanced viscosity formulation includes a pharmaceutically acceptable buffer. Sodium chloride or other tonicity agents are optionally used to adjust tonicity, if necessary.

By way of example only, the ophthalmically acceptable viscosity agent includes hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate. Other viscosity enhancing agents compatible with the targeted ocular site include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), *ceratonia*, chitin, carboxymethylated chitosan, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthum gum, gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), Splenda® (dextrose, maltodextrin and sucralose) or combinations thereof. In specific embodiments, the viscosity-enhancing excipient is a combination of MCC and CMC. In another embodiment, the viscosity-enhancing agent is a combination of carboxymethylated chitosan, or chitin, and alginate. The combination of chitin and alginate with the ophthalmic agents disclosed herein acts as a controlled release formulation, restricting the diffusion of the ophthalmic agents from the formulation. Moreover, the combination of carboxymethylated chitosan and alginate is optionally used to assist in increasing the permeability of the ophthalmic agents in the eye.

In some embodiments is an enhanced viscosity formulation, comprising from about 0.1 mM and about 100 mM of an ophthalmic agent, a pharmaceutically acceptable viscosity agent, and water for injection, the concentration of the viscosity agent in the water being sufficient to provide an enhanced viscosity formulation with a final viscosity from about 100 to about 100,000 cP. In certain embodiments, the viscosity of the gel is in the range from about 100 to about 50,000 cP, about 100 cP to about 1,000 cP, about 500 cP to

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about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 50,000 cP, about 10,000 cP to about 500,000 cP, about 15,000 cP to about 1,000,000 cP. In other embodiments, when an even more viscous medium is desired, the biocompatible gel comprises at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 70%, at least about 75%, or even at least about 80% or so by weight of the ophthalmic agent. In highly concentrated samples, the biocompatible enhanced viscosity formulation comprises at least about 25%, at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 75%, at least about 85%, at least about 90% or at least about 95% or more by weight of the ophthalmic agent.

In one embodiment, the pharmaceutically acceptable enhanced viscosity ophthalmically acceptable formulation comprises at least one ophthalmic agent and at least one gelling agent. Suitable gelling agents for use in preparation of the gel formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum and any combinations or mixtures thereof. In some other embodiments, hydroxypropylmethylcellulose (Methocel®) is utilized as the gelling agent. In certain embodiments, the viscosity enhancing agents described herein are also utilized as the gelling agent for the gel formulations presented herein.

In some embodiments, the ophthalmic gel composition described herein is an in situ gel formulation. In some instances, the in situ gel formation is based on increased pre-corneal residence time of the ophthalmic composition which improves ocular bioavailability, corneal mucoadhesion, lysosomal interaction and ionic gelation, improved corneal absorption, thermal gelation, or a combination thereof. In some instances, the in situ gel formulation is activated by pH, temperature, ion, UV, or solvent exchange.

In some instances, the ophthalmic gel composition comprises a muscarinic antagonist and one or more gelling agents. In some instances, the gelling agent includes, but is not limited to, poloxamer (e.g. Poloxamer 407), tetronics, ethyl (hydroxyethyl) cellulose, cellulose acetate phthalate (CAP), carbopol (e.g. Carbopol 1342P NF, Carbopol 980 NF), alginates (e.g. low acetyl gellan gum (Gelrite®)), gellan, hyaluronic acid, pluronics (e.g. Pluronic F-127), chitosan, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), dextran, hydroxy propyl methyl cellulose (HPMC), hydroxyethylcellulose (HEC), methylcellulose (MC), thiolated xyloglucan, polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, xyloglucans, or combinations thereof.

In some instances, the in situ gel formation further comprises a permeation enhancer. In some instances, the permeation enhancer includes surfactants (e.g. non-ionic surfactants), benzalkonium chloride, EDTA, surface-active heteroglycosides, calcium chelators, hydroxyl propyl beta cyclodextrin (HP beta CD), bile salts, and the like.

In some embodiments, other gel formulations are useful depending upon the particular ophthalmic agent, other pharmaceutical agent or excipients/additives used, and as such are considered to fall within the scope of the present disclosure. For example, other commercially-available glycerin-based gels, glycerin-derived compounds, conjugated, or crosslinked gels, matrices, hydrogels, and polymers, as well

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as gelatins and their derivatives, alginates, and alginate-based gels, and even various native and synthetic hydrogel and hydrogel-derived compounds are all expected to be useful in the ophthalmic agent formulations described herein. In some embodiments, ophthalmically acceptable gels include, but are not limited to, alginate hydrogels SAF®-Gel (ConvaTec, Princeton, N.J.), Duoderm® Hydro-active Gel (ConvaTec), Nu-gel® (Johnson & Johnson Medical, Arlington, Tex.); Carrasyn®(V) Acemannan Hydrogel (Carrington Laboratories, Inc., Irving, Tex.); glycerin gels Elta® Hydrogel (Swiss-American Products, Inc., Dallas, Tex.) and K-Y® Sterile (Johnson & Johnson). In further embodiments, biodegradable biocompatible gels also represent compounds present in ophthalmically acceptable formulations disclosed and described herein.

In some embodiments, the viscosity-enhancing agent is a cellulose-based polymer selected from cellulose gum, alkylcellulose, hydroxyl-alkyl cellulose, hydroxyl-alkyl alkylcellulose, carboxy-alkyl cellulose, or combinations thereof. In some embodiments, the viscosity-enhancing agent is hydroxyl-alkyl alkylcellulose. In some embodiment, the viscosity-enhancing agent is hydroxypropyl methylcellulose.

In certain embodiments, the enhanced viscosity formulation is characterized by a phase transition between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42° C.). In some embodiments, the phase transition occurs at 1° C. below body temperature, at 2° C. below body temperature, at 3° C. below body temperature, at 4° C. below body temperature, at 6° C. below body temperature, at 8° C. below body temperature, or at 10° C. below body temperature. In some embodiments, the phase transition occurs at about 15° C. below body temperature, at about 20° C. below body temperature or at about 25° C. below body temperature. In specific embodiments, the gelation temperature (Tgel) of a formulation described herein is about 20° C., about 25° C., or about 30° C. In certain embodiments, the gelation temperature (Tgel) of a formulation described herein is about 35° C., or about 40° C. Included within the definition of body temperature is the body temperature of a healthy individual, or an unhealthy individual, including an individual with a fever (up to -42° C.). In some embodiments, the pharmaceutical compositions described herein are liquids at about room temperature and are administered at or about room temperature.

Copolymers polyoxypropylene and polyoxyethylene (e.g. polyoxyethylene-polyoxypropylene triblock copolymers) form thermosetting gels when incorporated into aqueous solutions. These polymers have the ability to change from the liquid state to the gel state at temperatures close to body temperature, therefore allowing useful formulations that are applied to the targeted ocular site. The liquid state-to-gel state phase transition is dependent on the polymer concentration and the ingredients in the solution.

In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 15%, about 20%, about 25%, about 30%, about 35% or about 40% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24% or about 25% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 7.5% of the total

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weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 10% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 11% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 12% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 13% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 14% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 15% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 16% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 17% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 18% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 19% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 20% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 21% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 23% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 25% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 1%, about 5%, about 10%, or about 15% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, or about 5% of the total weight of the formulation.

In an alternative embodiment, the thermogel is a PEG-PLGA-PEG triblock copolymer (Jeong et al, *Nature* (1997), 388:860-2; Jeong et al, *J. Control. Release* (2000), 63:155-63; Jeong et al, *Adv. Drug Delivery Rev.* (2002), 54:37-51). The polymer exhibits sol-gel behavior over a concentration of about 5% w/w to about 40% w/w. Depending on the properties desired, the lactide/glycolide molar ratio in the PLGA copolymer ranges from about 1:1 to about 20:1. The resulting copolymers are soluble in water and form a free-flowing liquid at room temperature, but form a hydrogel at body temperature. A commercially available PEG-PLGA-PEG triblock copolymer is RESOMER RGP t50106 manufactured by Boehringer Ingelheim. This material is composed of a PLGA copolymer of 50:50 poly(DL-lactide-co-glycolide) and is 10% w/w of PEG and has a molecular weight of about 6000.

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Additional biodegradable thermoplastic polyesters include AtriGel® (provided by Atrix Laboratories, Inc.) and/or those disclosed, e.g., in U.S. Pat. Nos. 5,324,519; 4,938,763; 5,702,716; 5,744,153; and 5,990,194; wherein the suitable biodegradable thermoplastic polyester is disclosed as a thermoplastic polymer. Examples of suitable biodegradable thermoplastic polyesters include polylactides, polyglycolides, polycaprolactones, copolymers thereof, terpolymers thereof, and any combinations thereof. In some such embodiments, the suitable biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof. In one embodiment, the biodegradable thermoplastic polyester is 50/50 poly(DL-lactide-co-glycolide) having a carboxy terminal group; is present in about 30 wt. % to about 40 wt. % of the composition; and has an average molecular weight of about 23,000 to about 45,000. Alternatively, in another embodiment, the biodegradable thermoplastic polyester is 75/25 poly (DL-lactide-co-glycolide) without a carboxy terminal group; is present in about 40 wt. % to about 50 wt. % of the composition; and has an average molecular weight of about 15,000 to about 24,000. In further or alternative embodiments, the terminal groups of the poly(DL-lactide-co-glycolide) are either hydroxyl, carboxyl, or ester depending upon the method of polymerization. Polycondensation of lactic or glycolic acid provides a polymer with terminal hydroxyl and carboxyl groups. Ring-opening polymerization of the cyclic lactide or glycolide monomers with water, lactic acid, or glycolic acid provides polymers with the same terminal groups. However, ring-opening of the cyclic monomers with a monofunctional alcohol such as methanol, ethanol, or 1-dodecanol provides a polymer with one hydroxyl group and one ester terminal groups. Ring-opening polymerization of the cyclic monomers with a diol such as 1,6-hexanediol or polyethylene glycol provides a polymer with only hydroxyl terminal groups.

Since the polymer systems of thermosetting gels dissolve more completely at reduced temperatures, methods of solubilization include adding the required amount of polymer to the amount of water to be used at reduced temperatures. Generally after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostatic container at about 0-10° C. in order to dissolve the polymer. The mixture is stirred or shaken to bring about a more rapid dissolution of the thermosetting gel polymer. The ophthalmic agent and various additives such as buffers, salts, and preservatives are subsequently added and dissolved. In some instances the pharmaceutically agent is suspended if it is insoluble in water. The pH is modulated by the addition of appropriate buffering agents.

Ophthalmic Ointment Muscarinic Antagonist Composition

An ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (e.g. oil 80%-water 20%) with a high viscosity, intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that it contains. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an eye ointment), vulva, anus, and nose

The vehicle of an ointment is known as the ointment base. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are:

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hydrocarbon bases, e.g. hard paraffin, soft paraffin, micro-crystalline wax and ceresine; absorption bases, e.g. wool fat, beeswax; water soluble bases, e.g. macrogols 200, 300, 400; emulsifying bases, e.g. emulsifying wax, cetrimide; vegetable oils, e.g. olive oil, coconut oil, sesame oil, almond oil and peanut oil.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. In some embodiments, they are also derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases. The active agents are dispersed in the base, and later they get divided after the drug penetration into the target sites (e.g. membranes, skins, etc.).

The present disclosure recognizes that it is sometimes difficult to incorporate into the ointment a drug of low concentration with sufficient dose-to-dose uniformity for effectively treating a disorder or disease. In some embodiments, poly(ethylene-glycols), polyethoxylated castor oils (Cremophor®EL), alcohols having 12 to 20 carbon atoms or a mixture of two or more of said components are effective excipients for dispersing and/or dissolving effective amounts of ophthalmic drugs, in particular of ascomycins and staurosporine derivatives, in an ointment base, in particular in an ointment base substantially comprising oleaginous and hydrocarbon components, and that the resulting ointments are excellently tolerated by the skin and by ocular tissue.

The present disclosure further recognizes that ophthalmic drugs, such as a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), incorporated in the ointment compositions describes herein target the choroid and/or retina in a patient when the compositions are topically administered to the ocular surface, in particular to the sclera of said patient. In some embodiments, an ophthalmic ointment composition includes an ophthalmic drug, an ointment base and an agent for dispersing and/or dissolving said drug in the ointment base, selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components.

In some embodiments, the ointment bases include ophthalmically acceptable oil and fat bases, such as natural wax e.g. white and yellow bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax e.g. hard paraffin, microcrystalline wax; hydrocarbons e.g. liquid paraffin, white and yellow soft paraffin, white petrolatum, yellow petrolatum; or combinations thereof.

The above mentioned oil and fat bases are described in more detail, for instance, in the British Pharmacopoeia, Edition 2001, or the European Pharmacopoeia, 3rd Edition.

In some embodiments, the ointment base is present in amounts of about 50 to about 95, preferably of 70 to 90% by weight based on the total weight of the composition.

A preferred ointment base comprises a combination of one or more of one or more natural waxes like those indicated above, preferably wool wax (wool fat), and one or more hydrocarbons like those indicated above, preferably a soft paraffin or a petrolatum, more preferably in combination with liquid paraffin.

A special embodiment of the aforementioned ointment base comprises e.g. 5 to 17 parts by weight of wool fat, and 50 to 65 parts by weight of white petrolatum as well as 20 to 30 parts by weight of liquid paraffin.

In some embodiments, the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base is selected from a poly(ethylene-glycol), a polyethoxylated

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castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components. The agent is preferably used in amounts of 1 to 20 percent, more preferably 1 to 10 percent by weight of the entire semisolid ophthalmic composition.

Alcohols having 12 to 20 carbon atoms include particularly stearyl alcohol (C₁₈H₃₇OH), cetyl alcohol (C₁₆H₃₃OH) and mixtures thereof. Preferred are so-called cetostearyl alcohols, mixtures of solid alcohols substantially consisting of stearyl and cetyl alcohol and preferably comprising not less than 40 percent by weight of stearyl alcohol and a sum of stearyl alcohol and cetyl alcohol amounting to at least 90 percent by weight, and compositions comprising not less than 80 percent by weight of cetylstearyl alcohol and an emulsifier, in particular sodium cetostearyl sulfate and/or sodium lauryl sulfate, preferably in amounts not less than 7 percent by weight of emulsifier.

Polyethoxylated castor oils are reaction products of natural or hydrogenated castor oils and ethylene glycol. In some instances, such products are obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:30 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable and preferred is a product commercially available under the trade name Cremophor®EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an nD₂₅=ca.1.471. Also suitable for use in this category is, for instance, Nikkol®HCO-60, a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0° C.; Freezing point=ca. 32.4° C.; H₂O content (% KF)=ca. 0.03.

Poly(ethylene-glycols) are used in some embodiments as the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base according to the present disclosure. Suitable poly(ethylene-glycols) are typically mixtures of polymeric compounds of the general formula H—(OCH₂-CH₂)_nOH, wherein the index n typically range from 4 to 230 and the mean molecular weight from about 200 to about 10000. Preferably n is a number from about 6 to about 22 and the mean molecular weight between about 300 and about 1000, more preferably n ranges from about 6 to about 13 and the mean molecular weight from about 300 to about 600, most preferably n has a value of about 8.5 to about 9 and the relative molecular weight is about 400. Suitable poly(ethylene-glycols) are readily available commercially, for example poly(ethylene-glycols) having a mean molecular weight of about 200, 300, 400, 600, 1000, 1500, 2000, 3000, 4000, 6000, 8000 and 10000.

The poly(ethylene-glycols), in particular the preferred types described in the foregoing paragraph, are preferably used in amounts of 1 to 10, more preferably 1 to 5 percent by weight of the entire semisolid ophthalmic composition.

An especially preferred embodiment of the compositions according to the instant disclosure comprises an agent for dispersing and/or dissolving of the drug in the ointment base which is selected from a poly(ethylene-glycol), a polyethoxylated castor oil and preferably a mixture of said components.

Gel/Ointment Viscosity

In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10,000 to about 300,000 cps

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at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 15,000 to about 200,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 50,000 to about 150,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 70,000 to about 130,000 cps at about 20° C. and shear rate of 1 s⁻¹. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 90,000 to about 110,000 cps at about 20° C. and shear rate of 1 s⁻¹.

In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 1,000,000 centipoise, between about 750 and 1,000,000 centipoise; between about 1000 and 1,000,000 centipoise; between about 1000 and 400,000 centipoise; between about 2000 and 100,000 centipoise; between about 3000 and 50,000 centipoise; between about 4000 and 25,000 centipoise; between about 5000 and 20,000 centipoise; or between about 6000 and 15,000 centipoise. In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 50,000 and 1,000,000 centipoise.

In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

In some embodiments, the compositions described herein are viscous compositions at body temperature. In some embodiments, viscous compositions contain from about 10% to about 25% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 14% to about 22% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 15% to about 21% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 100,000 cP to about 1,000,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 150,000 cP to about 500,000 cP. In some embodi-

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ments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 250,000 cP to about 500,000 cP. In some of such embodiments, a viscous ophthalmic composition is a liquid at room temperature and gels at about between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42° C.). In some embodiments, a viscous ophthalmic composition is administered as monotherapy for treatment of an ophthalmic disease or condition described herein.

In some embodiments, the viscosity of the gel formulations presented herein is measured by any means described. For example, in some embodiments, an LVDV-II+CP Cone Plate Viscometer and a Cone Spindle CPE-40 is used to calculate the viscosity of the gel formulation described herein. In other embodiments, a Brookfield (spindle and cup) viscometer is used to calculate the viscosity of the gel formulation described herein. In some embodiments, the viscosity ranges referred to herein are measured at room temperature. In other embodiments, the viscosity ranges referred to herein are measured at body temperature (e.g., at the average body temperature of a healthy human).

Gel/Ointment Dose-to-Dose Uniformity

Typical ophthalmic gels are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. Furthermore, typical ophthalmic ointments are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

In some cases, described herein include ophthalmic gel compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some cases, described herein include ophthalmic ointment compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent con-

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centration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

Methods of Treatment

Disclosed herein are methods of arresting myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above. Also disclosed herein are methods of preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above.

In some embodiments, the ophthalmic aqueous formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous formulation includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic gel formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic ointment formulations described herein are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous formulation described herein is one drop of the aqueous composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodi-

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ments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

In some embodiments of the disclosed method, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 2° C., about 3° C., about 4° C., about 5° C., about 6° C., about 7° C., about 8° C., about 9° C., or about 10° C. prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 4° C. to about 8° C. prior to first use.

In some embodiments of the disclosed method, the ophthalmic composition is stored at room temperature after first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 16° C. to about 26° C. after to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 16° C., about 17° C., about 18° C., about 19° C., about 20° C., about 21° C., about 22° C., about 23° C., about 24° C., about 25° C., or about 26° C. after to first use.

In some embodiments, the ophthalmic aqueous formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of the aqueous formulation (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic gel formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of gel (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic ointment formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a small amount of ointment (approximately 0.25 inches) was applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years.

In some embodiments, the ophthalmic composition is administered in doses having a dose-to-dose ophthalmic agent concentration variation of less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

The number of times a composition is administered to an individual in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the individual’s response to the formulation. In some embodiments, a composition disclosed herein is administered once to an individual in need thereof with a mild acute condition. In some embodiments, a composition disclosed herein is administered more than once to an individual in need thereof with a moderate or severe acute

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condition. In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of an ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the ophthalmic agent is given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is from 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

Once improvement of the patient's ophthalmic conditions has occurred, a maintenance ophthalmic agent dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is optionally reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The amount of ophthalmic agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, according to the particular circumstances surrounding the case, including, e.g., the specific ophthalmic agent being administered, the route of administration, the condition being treated, the target area being treated, and the subject or host being treated. The desired dose is presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals.

In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

Kits/Articles of Manufacture

The disclosure also provides kits for preventing or arresting myopia development. Such kits generally will comprise one or more of the ophthalmic compositions disclosed herein, and instructions for using the kit. The disclosure also contemplates the use of one or more of the ophthalmic compositions, in the manufacture of medicaments for treating, abating, reducing, or ameliorating the symptoms of a disease, dysfunction, or disorder in a mammal, such as a human that has, is suspected of having, or at risk for developing myopia.

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In some embodiments, kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In other embodiments, the containers are formed from a variety of materials such as glass or plastic.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are also presented herein. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, drop bottles, tubes, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of ophthalmic compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that benefits by controlled release administration of an ophthalmic agent to the eye.

In some embodiments, a kit includes one or more additional containers, each with one or more of various materials (such as rinses, wipes, and/or devices) desirable from a commercial and user standpoint for use of a formulation described herein. Such materials also include labels listing contents and/or instructions for use and package inserts with instructions for use. A set of instructions is optionally included. In a further embodiment, a label is on or associated with the container. In yet a further embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In other embodiments a label is used to indicate that the contents are to be used for a specific therapeutic application. In yet another embodiment, a label also indicates directions for use of the contents, such as in the methods described herein.

In certain embodiments, the ophthalmic compositions are presented in a dispenser device which contains one or more unit dosage forms containing a compound provided herein. In a further embodiment, the dispenser device is accompanied by instructions for administration. In yet a further embodiment, the dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In another embodiment, such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In yet another embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

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EXAMPLES

Example 1—Ophthalmic Formulations

Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-8.

TABLE 1

Aqueous Solution Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 2

Aqueous Solution Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 3

Aqueous Solution Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.05-0.15	0.005-0.015 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	—	q.s. to 0.5-2.0 wt %
Deuterated Water	—	q.s. to 100 wt %

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TABLE 4

Mucus Penetrating Particle Formulation (Atropine)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	—	q.s. to formulate atropine at 0.001-0.05 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 5

Mucus Penetrating Particle Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Buffer agent and/or pD adjusting agent (e.g., borates and/or DCl)	—	q.s. for pD = 4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	—	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	—	q.s. to formulate atropine at 0.001-0.05 wt %
Deuterated Water	—	q.s. to 100 wt %

TABLE 6

Cellulose Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine Sulfate	0.01-0.5	0.001-0.05 (wt %)
Viscosity enhancing agent (e.g. hydroxypropyl methylcellulose)	10-50	1-5 (wt %)
Buffer agent and/or pD adjusting agent (e.g., sodium acetate and/or DCl)	—	q.s. for pD = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Deuterated Water	—	q.s. to 100 wt %

TABLE 7

Thermosetting Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Viscosity enhancing agent (e.g. poloxamer 407)	100-250	10-25 (wt %)

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TABLE 7-continued

Thermosetting Gel Formulation (Atropine Sulfate)		
Ingredient	Quantity (mg/g)	Concentration (wt %)
Buffer agent and/or pD adjusting agent (e.g., sodium acetate and/or DCl)	—	q.s. for pH = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Deuterated Water	—	q.s. to 100 wt %

TABLE 8

Ointment Formulation (Atropine Sulfate)		
Ingredient	Quantity (g) for 1000 mL solution	Concentration in 1000 mL aqueous solution
Atropine sulfate	0.01-0.5	0.001-0.05 (wt %)
Dispersing agent (e.g. polyethyleneglycol, and/or polyethoxylated castor oil and/or C12-C20 alcohol	10-200	1-20 (wt %)
Buffering agent pD adjusting agent (e.g. DCl)	—	q.s. for pD = 4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	—	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	—	q.s. 150-500 mOsm/L
Ointment base (e.g. wool wax and/or petrolatum and/or liquid paraffin)	—	q.s. to 100 wt %

Example 2—Preparation of an Aqueous Solution Formulation Containing 0.01% Atropine in D₂O

Stock 1% Solution

In a 100 mL solution, 1 gram of atropine, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) are added along with a quantity sufficient to equal 100 mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

Diluted 0.01% Solution

0.3 mL of the 1% solution was combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

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Example 3—Preparation of an Aqueous Solution Formulation Containing 0.01% Atropine Sulfate

Stock 1% Solution

In a 100 mL solution, 1 gram of atropine sulfate, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) were added along with a quantity sufficient to equal 100 mL sterile water for injection. The solution was mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders had dissolved and the solution became clear with no visible particles. Next, the stir bar was removed, and the solution was poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top was removed from the sterile stock bottle and the stock bottle was capped for storage with a sterile bottle cap.

Diluted 0.01% Solution

0.3 mL of the 1% solution was combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 4—Stability Analysis

Five 0.01% atropine sulfate solutions were prepared from the 1% atropine sulfate stock solution (preparation as described in Example 2). The pH of the five solutions was 5.87, 5.97, 5.90, 6.24, and 6.16 for solutions 1-5, respectively. Each solution was thoroughly mixed. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers according to Table 9.

TABLE 9

Container Filling Outline		
Type of Container	Volume of 0.01% Atropine Sulfate Drug Product in Container	Total Containers Filled
Sterile Eyedroppers	5-mL	12
Sterile Glass Vials	5-mL	12

The samples were then stored at different conditions for stability analysis. The samples were analyzed at different time points up to 2 months. The storage conditions include: 40° C. with 75% relative humidity (RH) (samples were transferred from 2-8° C. condition after 3 days), 25° C. with 60% RH, and 60° C. The time points were 1 week, 2 weeks, 1 month, and 2 months. At each of the time point, one plastic eyedropper (LDPE plastic) and one glass vial from each of the stored condition were removed and allowed to equilibrate to ambient conditions. Once equilibrated, both the plastic eyedropper and the glass vials were inverted 3 times. The solution in the eyedroppers was transferred to an HPLC vial in a drop wise fashion through the dropper. The solution in the glass vial was aliquotted into an HPLC vial using a glass Pasteur pipette. The samples were then tested for purity and potency using the UPLC method listed in Table 10.

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TABLE 10

UPLC Method Parameters	
Parameter	Condition
Column	EMD, Hiber HR PurospherSTAR C-18, 100 × 2.1 mm, 2 µm
Mobile Phase/Diluent	87:13, 50 mM Potassium Phosphate: Acetonitrile, pH 3.5
Flow	Isocratic
Flow Rate	0.5 mL/min
Detection Wavelength	210 nm
Column Temperature	30 ± 3° C.

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TABLE 10-continued

UPLC Method Parameters	
Parameter	Condition
Autosampler Temperature	5 ± 3° C.
Run Time	6.0 minutes
Injection Volume	10 µL*
Needle Wash Solution	90/10 Water:Acetonitrile

10 *Modified from original method to maintain sensitivity at 100 µg/mL nominal.

Table 11 lists the stability data for the 0.01% atropine sulfate solutions.

TABLE 11

Stability Data for 0.01% Atropine Sulfate Solutions														
		Purity	Potency	pH	Purity	Potency	Purity	Potency	Purity	Potency	pH	Purity	Potency	pH
1	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.5	99.8	5.9	ND	ND	99.1	99.9	ND	ND	ND	95.4	97.4
		40° C./75% RH				ND	ND	96.2	97.3	95.1	95.6	5.2	ND	ND
		60° C.				80.8	833	86.2	88.6	88.3	91.5	4.2	ND	ND
	Glass Vial	25° C./60% RH	99.8	100.4	ND	ND	ND	92.2	93.1	80.7	80.5	7.8	73.0	74.5
		40° C./75% RH				ND	ND	73.6	74.1	50.1	50.2	7.4	ND	ND
		60° C.				43.1	439	28.3	28.4	ND	ND	ND	ND	ND
	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.7	99.9	6.0	ND	ND	991	996	ND	ND	ND	97.0	99.1
		40° C./75% RH				ND	ND	96.6	97.2	95.5	95.8	5.6	ND	ND
		60° C.				89.4	92.2	92.2	94.0	90.6	94.4	4	ND	ND
	Glass Vial	25° C./60% RH	99.8	100.2	ND	ND	ND	92.6	92.9	82.5	82.2	7.6	80.2	81.6
		40° C./75% RH				ND	ND	74.7	75.1	59.1	59.0	7.2	ND	ND
		60° C.				54.2	55.2	37.3	37.4	ND	ND	ND	ND	ND
3	Eye dropper, LDPE (Plastic)	25° C./60% RH	99.3	96.3	5.9	ND	ND	98.7	96.1	ND	ND	ND	95.8	94.8
		40° C./75% RH				ND	ND	96.7	93.1	94.8	91.8	5.5	ND	ND
		60° C.				88.8	89.0	88.0	86.8	88.6	87.7	4.1	ND	ND
	Glass Vial	25° C./60% RH	99.4	98.4	ND	ND	ND	94.1	912	85.0	81.9	7.5	79.3	78.3
		40° C./75% RH				ND	ND	72.2	746	61.3	63.0	7.2	ND	ND
		60° C.				48.6	51.1	34.1	34.9	ND	ND	ND	ND	ND
	Eyedropper, LDPE (Plastic)	25° C./60% RH	99.8	99.6	6.2	ND	ND	99.1	988	ND	ND	ND	96.4	97.6
		40° C./75% RH				ND	ND	96.3	970	94.5	94.2	5.6	ND	ND
		60° C.				90.5	93.0	89.3	90.6	84.2	85.8	4.2	ND	ND
	Glass Vial	25° C./60% RH	99.8	98.8	ND	ND	ND	90.7	900	769	75.1	7.6	72.5	71.6
		40° C./75% RH				ND	ND	71.0	68.7	57.0	56.7	7.2	ND	ND
		60° C.				52.4	52.1	29.7	28.6	ND	ND	ND	ND	ND
5	Eyedropper LDPE (Plastic)	25° C./60% RH	99.6	100.5	6.2	ND	ND	99.3	100.4	ND	ND	ND	97.8	100.5
		40° C./75% RH				ND	ND	95.9	96.7	96.8	97.6	5.5	ND	ND
		60° C.				91.2	94.6	91.4	93.6	90.3	92.8	4.2	ND	ND
	Glass Vial	25° C./60% RH	99.8	100.7	ND	ND	ND	90.5	91.3	79.3	79.7	7.8	72.8	74.6
		40° C./75% RH				ND	ND	71.3	71.9	56.0	56.4	7.3	ND	ND
		60° C.				46.3	47.4	29.5	29.6	ND	ND	ND	ND	ND

¹The 25° C. and the 60° C. samples were pulled at 15 days, the 40° C. samples were pulled at 11 days.

²The 25° C. and the 60° C. samples were pulled at 28 days, the 40° C. samples were pulled at 24 days.

³The 25° C. and the 60° C. samples were pulled at 46 days.

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A change in the pH of the 0.01% Atropine Sulfate solutions was observed over the course of the stability study. The plastic (LDPE) eyedroppers maintained pH around 6.2 when stored at 25° C. for 2 months. However at the same time point, the pH of the 0.01% atropine has increased to 7.2 when stored in glass vials. Additionally, when stored at elevated temperatures (e.g. 40° C. and 60° C.), the pH in the plastic (LDPE) eyedroppers dropped to approximately 4-5, while the pH maintained around 7.2 when stored in the glass vials.

There was also a significant difference in the rate of degradation for Atropine Sulfate (0.01%) when stored in plastic (LDPE) eyedroppers versus Type I glass vials. However, in both containers there was an increase of an early eluting related substance at relative retention time (RRT) =0.87-0.89. In some cases, this early eluting related substance is referred to as primary degradant. In some instances, the primary degradant is referred to as RRT 0.87-0.89. This related substance is likely to be the first parameter to fail specification regardless of the container. The amount of this related substance was tracked at each time point and is listed in Table 12.

TABLE 12

Area (%) of the Main Degradation Species for 0.01% Atropine Sulfate (RRT 0.87-0.89)						
Analyst	Temperature ° C.	t = 0	t = 1 week	t = 2 week	t = 1 month	t = 2 months
1	25	0.08	NA	0.92	NA	3.98
	40	NA	NA	3.74	4.78	NA
	60	NA	17.78	13.49	11.51	NA
2	25	0.07	NA	0.88	NA	2.46
	40	NA	NA	3.26	4.37	NA
	60	NA	9.38	7.67	9.13	NA
3	25	0.07	NA	1.05	NA	2.88
	40	NA	NA	2.98	4.85	NA
	60	NA	9.59	11.57	10.55	NA
4	25	0.08	NA	0.92	NA	3.09
	40	NA	NA	3.43	5.32	NA
	60	NA	8.30	10.46	15.49	NA
5	25	0.08	NA	0.64	NA	1.66
	40	NA	NA	3.96	3.07	NA
	60	NA	7.61	8.35	9.7	NA
Average 25° C.		0.08	NA	0.88	NA	2.81
Average 40° C.		NA	NA	3.47	4.48	NA
Average 60° C.		NA	10.53	10.31	11.28	NA

Arrhenius based shelf life predictions were calculated using the related substance data from Table 12. These predictions are based on an assumption that the degradation is first order (linear). These predictions are illustrated in FIGS. 1 and 2. FIG. 1 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 40° C. The pH range of the atropine sulfate solution is from 5.9-6.2. FIG. 2 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25° C. and 60° C. The pH range of the atropine sulfate solution is from 5.9-6.2.

Example 5-1% Atropine Sulfate (Bausch+Lomb) Sample Analysis

The 1% atropine sulfate sample was obtained from Bausch+Lomb (Lot 198421). For comparison the pH of the 1% Atropine Sulfate drug product was determined in the neat solution as well as a sample that was diluted to the

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current nominal concentration (0.01% Atropine Sulfate) using the vehicle. Additionally a sample was diluted to the nominal concentration with method diluent. Both samples diluted to the nominal concentration were analyzed using the RP-UPLC method (Table 10). The results are listed in Table 13.

TABLE 13

pH and Purity of the Bausch + Lomb Atropine Sulfate Sample		
Sample	pH	Purity (% area)
1% Atropine Sulfate	4.89	ND
0.01% Atropine Sulfate, diluted with Vehicle	6.16	99.6%
0.01% Atropine Sulfate, diluted with Diluent	ND	99.6%
Vehicle	7.94	ND

ND = not determined

Example 6—Dose Uniformity (10-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 10 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 7—Dose Uniformity (5-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 5 drops of the aqueous composition are dispensed from each bottle at predetermined time inter-

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vals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 8—Dose Uniformity (2-Dose)

To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 2 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 9—Formulation Stability Comparison

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Eight formulations illustrated in Table 14A were analyzed at t=0, 2 weeks, and 4 weeks. A RP-HPLC method was used to carry out the analysis.

TABLE 14A

Atropine sulfate formulations							
Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	—	4.2	SWFI
2	0.025	0.01	0.90	0.01	—	4.2	SWFI
3	0.010	0.01	0.90	0.01	—	4.8	SWFI
4	0.025	0.01	0.90	0.01	—	4.8	SWFI
5	0.010	0.01	0.90	—	0.04	5.8	SWFI
6	0.025	0.01	0.90	—	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	—	5.2 (pD)	D ₂ O
8	0.010	0.01	0.90	—	0.04	6.2 (pD)	D ₂ O

The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware. The pD of Formulation 7 and Formulation 8 are 5.2 and 6.2, respectively. In some instances, the pD is calculated as $pD=0.4+pH^*$, in which pH^* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

Table 14B illustrates analysis time points for the formulations listed in Table 14A.

TABLE 14B

Schedule for atropine sulfate formulation testing			
Storage	Time Point		
Condition (Horizontal)	Initial (t = 0)	2 Week	4 Week
25° C./60% RH	X	X	X
40° C./75% RH		X	X
60° C.		X	X

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Table 15 illustrates the atropine sulfate purity data associated with each of the eight formulations. Purity is indicated as percentage of area under the curve.

TABLE 15

Atropine sulfate purity as Area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks ¹
10 Formulation 1 pH 4.2	25/60	97.39	97.76	98.20
	40/75		97.25	97.04
	60° C.		94.98	93.87
15 Formulation 2 pH 4.2	25/60	98.85	99.03	99.08
	40/75		98.50	98.32
	60° C.		97.47	96.65
15 Formulation 3 pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60° C.		95.94	94.65
20 Formulation 4 pH 4.8	25/60	98.81	98.75	98.46
	40/75		98.26	98.01
	60° C.		96.22	94.04
20 Formulation 5 pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60° C.		80.94	66.83
25 Formulation 6 pH 5.8	25/60	99.08	98.91	98.46
	40/75		97.65	96.20
	60° C.		89.15	80.68
25 Formulation 7 pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60° C.		96.70	94.01

TABLE 15-continued

Atropine sulfate purity as Area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks ¹
50 Formulation 8 pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60° C.		95.97	92.72

¹Some chromatographic interference were observed to occur late in the run (~27-32 minutes) for many of the t = 4 week stability samples and in some instances is proposed to be system related.

After four weeks of storage at 60° C., in some instances the atropine sulfate concentration have an impact on the stability for the formulations containing acetic acid at pH 4.2. For example, atropine sulfate concentration at 0.025% w/v (Formulation 2) showed a 2.8% increase in % purity at pH 4.2 compared to the atropine sulfate concentration at 0.010% w/v (Formulation 1). This trend was not observed for the acetic acid formulations at pH 4.8 (Formulations 3 and 4); rather a 0.6% decrease in % purity was observed for the higher doses.

The dose dependent stability trend that was observed at pH=4.2 was also seen in the formulations containing citric

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acid at pH 5.8 (Formulations 5 and 6). After four weeks of storage at 60° C. there is approximately 14% less degradation in the higher does than observed in the lower dose.

At both the high and the low doses, more degradation is observed in the formulations that start at a higher pH. This degradation is predominantly the growth of tropic acid. In some instances, buffer species plays a role in the observed degradation between the different pH values.

The percentage of tropic acid observed for each of the formulations at t=4 weeks and at 60° C. are as follow:

- Formulation 1—Tropic acid observed is 0.54%.
- Formulation 2—Tropic acid observed is 0.93%.
- Formulation 3—Tropic acid observed is 1.58%.
- Formulation 4—Tropic acid observed is 3.03%.
- Formulation 5—Tropic acid observed is 29.13%.
- Formulation 6—Tropic acid observed is 16.84%.
- Formulation 7—Tropic acid observed is 1.07%.
- Formulation 8—Tropic acid observed is 4.03%.

In some embodiments, switching the water source to deuterated water (D₂O) has an impact on stabilizing the growth of the tropic acid peak for the formulation containing acetic acid at pD 5.2 (Formulation 7), see FIG. 4. In addition, in the formulation containing citric acid at pD 6.2 (Formulation 8), the deuterated water also stabilizes atropine sulfate, see FIG. 5.

Table 16 illustrates tropic acid as area under the curve for each of the eight formulations. Tropic acid is a degradant of atropine sulfate. In some instances, LOQ was previously found to be 0.05% for the RP-HPLC method.

TABLE 16

Tropic acid as area-%				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 pH 4.2	25/60	<LOQ	0.08	<LOQ
	40/75		0.10	0.10
	60° C.		0.37	0.51
Formulation 2 pH 4.2	25/60	<LOQ	0.05	<LOQ
	40/75		0.11	0.12
	60° C.		0.46	0.93
Formulation 3 pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60° C.		0.90	1.58
Formulation 4 pH 4.8	25/60	<LOQ	0.10	0.13
	40/75		0.31	0.53
	60° C.		1.84	3.03
Formulation 5 pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60° C.		16.62	29.13
Formulation 6 pH 5.8	25/60	<LOQ	0.24	0.42
	40/75		1.30	2.44
	60° C.		9.32	16.84
Formulation 7 pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60° C.		0.71	1.07
Formulation 8 pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60° C.		2.32	4.03

Table 17 illustrates percentage of potency of atropine in the eight formulations.

TABLE 17

% Potency				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 pH 4.2	25/60	109.4	110.3	112.8
	40/75		111.0	112.4
	60° C.		112.8	114.8

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TABLE 17-continued

% Potency				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 2 pH 4.2	25/60	102.9	107.1	109.7
	40/75		108.4	109.6
	60° C.		109.4	111.0
Formulation 3 pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60° C.		108.0	109.9
Formulation 4 pH 4.8	25/60	102.5	107.9	109.2
	40/75		107.4	108.9
	60° C.		107.9	108.8
Formulation 5 pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60° C.		90.2	77.7
Formulation 6 pH 5.8	25/60	107.2	107.1	109.1
	40/75		106.8	107.1
	60° C.		99.0	93.7
Formulation 7 pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60° C.		111.8	113.5
Formulation 8 pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60° C.		101.6	103.0

After 4 weeks of storage, the observed potency values were elevated from the t=0 and 2 week time points, with the exception of Formulations 5 and 6 at 60° C. where the potencies dropped due to degradation. In some instances, these potency values are within the error of the HPLC method, but appear to be trending upward. Mass balance was calculated for the 60° C. data and results were consistent across the formulations and levels of degradation, although skewed lower due to the higher than anticipated potency values at 4 weeks, see FIG. 3.

Table 18 illustrates pH or pD stability of the eight formulations.

TABLE 18

pH/pD Stability				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 1 (pH)	25/60	4.21	3.93	4.02
	40/75		3.86	3.96
	60° C.		3.71	3.86
Formulation 2 (pH)	25/60	4.26	4.11	4.25
	40/75		4.04	4.17
	60° C.		3.93	4.10
Formulation 3 (pH)	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60° C.		4.32	4.40
Formulation 4 (pH)	25/60	4.98	4.93	5.05
	40/75		4.89	4.98
	60° C.		4.77	4.77
Formulation 5 (pH)	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60° C.		5.82	5.78
Formulation 6 (pH)	25/60	5.80	5.69	5.77
	40/75		5.65	5.67
	60° C.		5.54	5.50
Formulation 7 (pD)	25/60	<i>5.31</i>	<i>5.10</i>	<i>5.24</i>
	40/75		<i>5.08</i>	<i>5.15</i>
	60° C.		<i>5.00</i>	<i>4.93</i>
Formulation 8 (pD)	25/60	<i>6.25</i>	<i>5.72</i>	<i>5.88</i>
	40/75		<i>5.74</i>	<i>5.78</i>
	60° C.		<i>5.58</i>	<i>5.50</i>

The italicized values are pD values for a deuterated sample. In some embodiments, the pD of the deuterated samples are pD=pH_{reading}+0.4 (Glasoe, et al. "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

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At the two lower temperatures, the pH values at t=4 week are slightly elevated from the t=2 week time point. These data were generated using a new glass pH probe. In some instances, the observed differences are due to the probe differences or additional variables such as for example, the age of the standard buffers or temperature gradients within the laboratory environment. The downward pH trend for each formulation with increasing temperatures at t=4 week is consistent with previous data and is consistent with the increase in the amount of tropic acid present in the stability sample.

Example 10-Determination of Shelf Life and Activation Energy

Activation energy was calculated for the eight formulations disclosed in Example 9 and comparison with a reference standard was made with Formulations 4-7.

Table 19 illustrates the activation energy (Ea) calculation. The Ea minimum is 17.8 Kcal/mol, the Ea maximum is 21.3 Kcal/mol, and the Ea mean is 19.5 Kcal/mol. Mean is $\pm 3 \times \text{stdev}$. FIGS. 6 and 7 illustrate the poor correlation between RS and tropic acid with Formulation 4 and Formulation 7, respectively. FIGS. 8 and 9 illustrate improved correlation between RS and tropic acid with Formulation 5 and Formulation 6, respectively. At a lower pH (e.g. pH 4.8 or lower), there was a poor correlation observed (Formulation 4 and Formulation 7). This was due to a slowed hydrolysis and increased alternative degradation pathways. At a higher pH (e.g., pH 5.8 or higher), an improved or better correlation was observed (Formulation 5 and Formulation

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6). This was due to the hydrolysis of atropine as the primary degradant. It is noted that the activation energy is for the specific acid catalyzed degradation to tropic acid-the predominant degradation product and degradation mechanism operating at pH 5.8 or higher.

TABLE 19

Activation energy for total related substance (RS) and tropic acid			
	Total RS	Tropic Acid	
1	Poor Corr	Poor Corr	
2	12.2	Poor Corr	
3	Poor Corr	18.3	
4	16.8	18.1	
5	19.8	19.7	
6	19.2	20.0	
7	13.2	15.5	
8	Poor Corr	18.9	
Mean	16.2	18.4 Kcal/mole	
Stdev	3.4	1.6	
RSD	21%	9%	

Table 20 illustrates the rate of RS or tropic acid formation per week at 40° C.

TABLE 20

		Rate 40° C. (total RS %/wk)	Rate 40° C. (Tropic acid %/wk)
Formulation			
Formulation 5	0.01% Atr Citrate pH 5.8	1.16	1.09
Formulation 6	0.025% Atr Citrate pH 5.8	0.72	0.61
Formulation 8	0.01% Atr Citrate pD 6.2 D ₂ O		0.163

Table 21 illustrates the activation energy and predicted shelf life at 30° C. calculated based on Table 20. It is assumed for the calculation that tropic acid and total RS is 5% (self-life).

TABLE 21A

Rate @30° C. (Total RS %/wk)				Estimated Shelf life @30° C. (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.45	0.41	0.38	2.78	3.04	3.33
6	0.28	0.26	0.23	4.47	4.90	5.37
8	—	—	—	—	—	—

TABLE 21B

Rate @30° C. (Tropic acid %/wk)				Estimated Shelf life @30° C. (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.42	0.39	0.35	2.95	3.24	3.54
6	0.24	0.22	0.20	5.28	5.78	6.33
8	0.06	0.06	0.05	19.75	21.64	23.70

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At pD 6.2, the deuterated formulation (Formulation 8) has a predicted shelf life of close to 2 years at 30° C.

Table 22 illustrate the predicted shelf life at temperatures of 40° C, 30° C., 25° C., and 2-8° C. for Formulations 4-8 for total RS and tropic acid, respectively.

TABLE 22

Stability Prediction				Temp-		
Formu- lation	Temperature (° C.)	RS		erature (° C.)	Tropic Acid	
		weeks	months		weeks	months
4	40	16.5	4.1	40	7.7	1.9
	30	40.2	10.1	30	20.0	5.0
	25	64.2	16.0	25	33.0	8.3
5	2-8	493.4	123.4	2-8	296.8	74.2
	40	2.8	0.7	40	0.9	0.2
	30	7.9	2.0	30	2.7	0.7
6	25	13.7	3.4	25	4.6	1.2
	2-8	151.1	37.8	2-8	50.5	12.6
	40	5.8	1.4	40	1.7	0.4
7	30	15.9	4.0	30	4.8	1.2
	25	27.3	6.8	25	8.4	2.1
	2-8	281.6	70.4	2-8	95.9	24.0
8	40	11.5	2.9	40	16.9	4.2
	30	23.2	5.8	30	38.4	9.6
	25	33.4	8.4	25	59.1	14.8
8	2-8	165.7	41.4	2-8	388.2	97.1
	40	—	—	40	6.2	1.6
	30	—	—	30	17.0	4.3
8	25	—	—	25	28.9	7.2
	2-8	—	—	2-8	287.1	71.8

Example 11—Additional Formulation Stability Comparison

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Thirteen formulations illustrated in Table 23A were analyzed. Formulations 1-8 had been analyzed at t=0, 2 weeks, 4 weeks, and 8 weeks. Formulations 9-13 had been analyzed at t=0, 2 weeks, and 4 weeks. The pH values reported herein are the measured pH values obtained using the Thermo Scientific, Orion Dual Star pH/ISE benchtop pH meter and the Orion Double Junction Micro pH probe S/N S01-18520 calibrated with H₂O based standards.

TABLE 23A

Atropine sulfate Formulations							
Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	—	4.2	SWFI
2	0.025	0.01	0.90	0.01	—	4.2	SWFI
3	0.010	0.01	0.90	0.01	—	4.8	SWFI
4	0.025	0.01	0.90	0.01	—	4.8	SWFI
5	0.010	0.01	0.90	—	0.04	5.8	SWFI
6	0.025	0.01	0.90	—	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	—	5.2 (pD)	D ₂ O
8	0.010	0.01	0.90	—	0.04	6.2 (pD)	D ₂ O
9	0.010	—	0.90	—	0.04	6.8 (pD)	D ₂ O
10	0.010	—	0.90	—	0.04	6.4	H ₂ O (control)
11	0.010	—	0.90	—	0.08	6.4	H ₂ O (control)
12	0.010	—	0.90	—	0.04	7.2 (pD)	D ₂ O
13	0.010	—	0.90	—	0.04	6.8	H ₂ O (control)

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The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware and filled into LDPE eye droppers. In some instances, the pD is calculated as pD=0.4+pH*, in which pH* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

Table 23B illustrates analysis time points for the formulations listed in Table 23A.

TABLE 23B

Schedule for atropine sulfate formulation testing			
Storage Condition (Horizontal)	Time Point		
	Initial (t = 0)	2 Week	4 Week
25° C./60% RH	X	X	X
40° C./75% RH		X	X
60° C.		X	X

Table 24A and Table 24B illustrate atropine sulfate purity data associated with the atropine sulfate formulations. Purity is indicated as percentage of area under the curve. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 24A

Atropine Sulfate Purity as Area-% for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60° C.		95.94	94.65
Formulation 5 ↓C H ₂ O pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60° C.		80.94	66.83
Formulation 10 ↓C H ₂ O pH 6.4	25/60	98.66	96.67	95.81
	40/75		91.07	85.27
	60° C.		59.77	42.87
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	99.47	97.87	96.69
	40/75		90.97	84.26
	60° C.		54.96	34.40
Formulation 13 ↓C H ₂ O pH 6.8	25/60	97.21	95.42	93.24
	40/75		83.05	73.00
	60° C.		43.99	27.50

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TABLE 24B

Atropine Sulfate Purity as Area-% for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	98.93	99.07	98.39
↓A D ₂ O pD 5.2	40/75		98.51	97.55
	60° C.		96.70	94.01
Formulation 8	25/60	98.93	98.95	98.51
↓C D ₂ O pD 6.2	40/75		98.53	97.44
	60° C.		95.97	92.72
Formulation 9	25/60	99.29	98.42	98.07
↓C D ₂ O pD 6.8	40/75		95.20	93.22
	60° C.		75.17	65.97
Formulation 12	25/60	98.53	97.17	95.99
↓C D ₂ O pD 7.2	40/75		90.75	84.64
	60° C.		56.78	46.05

Table 25A and Table 25B illustrate tropic acid formation associated with the atropine sulfate formulations. Tropic acid is a degradant of atropine sulfate, and is indicated as percentage of area under the curve. LOQ was found to be 0.05% for the RP-HPLC method. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid, respectively.

TABLE 25A

Tropic Acid as Area-% for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	<LOQ	0.12	0.05
↓A H ₂ O pH 4.8	40/75		0.19	0.27
	60° C.		0.90	1.58
Formulation 5	25/60	<LOQ	0.40	0.71
↓C H ₂ O pH 5.8	40/75		2.22	4.35
	60° C.		16.62	29.13
Formulation 10	25/60	0.74	1.90	3.21
↓C H ₂ O pH 6.4	40/75		7.61	13.49
	60° C.		37.44	54.06
Formulation 11	25/60	0.09	1.31	2.64
↓C(2x) H ₂ O pH 6.4	40/75		7.61	14.68
	60° C.		42.43	62.23
Formulation 13	25/60	2.21	3.66	6.11
↓C H ₂ O pH 6.8	40/75		15.47	25.80
	60° C.		53.24	69.34

TABLE 25B

Tropic Acid as Area-% for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	<LOQ	0.07	0.08
↓A D ₂ O pD 5.2	40/75		0.14	0.24
	60° C.		0.71	1.07
Formulation 8	25/60	<LOQ	0.11	0.14
↓C D ₂ O pD 6.2	40/75		0.33	0.65
	60° C.		2.32	4.03
Formulation 9	25/60	0.06	0.55	1.06
↓C D ₂ O pD 6.8	40/75		3.16	6.29
	60° C.		21.09	29.25
Formulation 12	25/60	0.42	1.35	2.62
↓C D ₂ O pD 7.2	40/75		7.27	13.53
	60° C.		38.58	48.15

Table 26A and Table 26B illustrate the percentage of potency of atropine in the formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

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TABLE 26A

Percentage of potency for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	106.3	108.0	109.6
↓A H ₂ O pH 4.8	40/75		108.1	110.0
	60° C.		108.0	109.9
Formulation 5	25/60	105.0	105.9	107.1
↓C H ₂ O pH 5.8	40/75		103.8	103.5
	60° C.		90.2	77.7
Formulation 10	25/60	101.7	100.0	98.0
↓C H ₂ O pH 6.4	40/75		89.4	87.0
	60° C.		63.7	45.7
Formulation 11	25/60	97.5	96.1	94.3
↓C(2x) H ₂ O pH 6.4	40/75		89.4	82.0
	60° C.		55.7	35.20
Formulation 13	25/60	99.4	96.9	94.1
↓C H ₂ O pH 6.8	40/75		85.0	74.0
	60° C.		46.4	29.8

TABLE 26B

Percentage of potency for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	107.3	111.3	112.9
↓A D ₂ O pD 5.2	40/75		111.6	113.5
	60° C.		111.8	113.5
Formulation 8	25/60	99.0	103.0	105.0
↓C D ₂ O pD 6.2	40/75		104.9	104.7
	60° C.		101.6	103.0
Formulation 9	25/60	101.4	99.9	100.1
↓C D ₂ O pD 6.8	40/75		97.4	93.2
	60° C.		78.7	68.9
Formulation 12	25/60	104.9	103.5	101.6
↓C D ₂ O pD 7.2	40/75		96.9	89.1
	60° C.		62.5	50.9

Table 27A and Table 27B illustrate the stability of pH or pD for the atropine sulfate formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

TABLE 27A

Stability of pH for H ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 3	25/60	4.85	4.44	4.61
↓A H ₂ O pH 4.8	40/75		4.41	4.54
	60° C.		4.32	4.40
Formulation 5	25/60	5.87	5.93	6.03
↓C H ₂ O pH 5.8	40/75		5.96	5.96
	60° C.		5.82	5.78
Formulation 10	25/60	6.43	6.41	6.46
↓C H ₂ O pH 6.4	40/75		6.62	6.67
	60° C.		6.01	5.92
Formulation 11	25/60	6.44	6.47	6.72
↓C(2x) H ₂ O pH 6.4	40/75		6.66	6.61
	60° C.		6.27	6.23
Formulation 13	25/60	6.77	6.91	6.91
↓C H ₂ O pH 6.8	40/75		6.65	6.62
	60° C.		6.30	6.19

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TABLE 27B

Stability of pD for D ₂ O Formulations				
Solvent	Condition	t = 0	t = 2 weeks	t = 4 weeks
Formulation 7	25/60	5.31	5.10	5.24
↓A D ₂ O pD 5.2	40/75		5.08	5.15
	60° C.		5.00	4.93
Formulation 8	25/60	6.25	5.72	5.88
↓C D ₂ O pD 6.2	40/75		5.74	5.78
	60° C.		5.58	5.50
Formulation 9	25/60	6.76	6.80	6.81
↓C D ₂ O pD 6.8	40/75		6.78	6.86
	60° C.		6.45	6.24
Formulation 12	25/60	7.25	7.18	7.26
↓C D ₂ O pD 7.2	40/75		7.14	7.15
	60° C.		6.52	6.36

Example 12. Determination of Shelf Life and
Activation Energy for Atropine Sulfate
Formulations of Example 11

Activation energy was calculated for the atropine sulfate formulations disclosed in Example 11. Specifically, activation energies were calculated from the total % of related substances (RS) at 40° C. and 60° C. (2 point calculations) and from tropic acid formation at 40° C. and 60° C. (2 point calculations). These values were then averaged. Table 28 illustrates the activation energy calculation. Table 29 illustrates estimated shelf-lives from the 40° C. rate of formation of % RS and tropic acid, respectively. FIG. 10 illustrates estimated shelf lives for D₂O and H₂O formulations.

TABLE 28

Activation Energy		
Atropine Formulations	Total RS	Tropic Acid
7	14	19
3	16	17
8	20	21
5	14	Poor Corr
6	15	16
Mean	16.3	18.7
Stdev	2.68	1.90
RSD	16%	10%
Poor Corr:	One or more curve had R ² < 0.95	

TABLE 29

Estimated Shelf Life				
Estimated Shelf life/mo				
Total related substances % (limit = 8%)		Tropic acid % (limit = 5%)		
Formulation	8° C.	25° C.	8° C.	25° C.
0.01% w/v Atr	189	26	1427	147
0.01% w/v Acetate				
0.9% w/v NaCl				
0.01% w/v BAK				
pD 5.2 D ₂ O (Formulation 7)				
0.01% w/v Atr	211	29	1095	113
0.01% w/v Acetate				
0.9% w/v NaCl				
0.01% w/v BAK				
pH 4.8 H ₂ O (Formulation 3)				

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TABLE 29-continued

Estimated Shelf Life				
Estimated Shelf life/mo				
Total related substances % (limit = 8%)		Tropic acid % (limit = 5%)		
Formulation	8° C.	25° C.	8° C.	25° C.
0.01% w/v Atr	158	22	369.8	38
0.04% w/v Citrate				
0.9% w/v NaCl				
0.01% w/v BAK				
pD 6.2 D ₂ O (Formulation 8)				
0.01% w/v Atr	37	5.2	54	5.5
0.04% w/v Citrate				
0.9% w/v NaCl				
0.01% w/v BAK				
pH 5.8 H ₂ O (Formulation 5)				
0.01% Atr	13.6	2.6		
0.9% w/v NaCl				
pH 5.9 H ₂ O extemporaneous preparation				

Table 30 illustrates the predicted shelf life at temperatures of 40° C., 30° C., 25° C., and 2-8° C. for Formulations 2-8 for total RS and tropic acid, respectively.

TABLE 30

Stability Prediction				Temp-		
Formu- lation	Temperature (° C.)	RS		erature (° C.)	Tropic Acid	
		weeks	months		weeks	months
2	40	64.5	16.1	40	—	—
	30	153.2	38.3	30	—	—
	25	241.2	60.3	25	—	—
3	2-8	1747.9	437.0	2-8	—	—
	40	31.1	7.8	40	99.5	24.9
	30	73.9	18.5	30	268.3	67.1
	25	116.3	29.1	25	451.8	113.0
4	2-8	842.9	210.7	2-8	4382.0	1095.5
	40	30.7	7.7	40	42.1	10.5
	30	73.0	18.2	30	113.7	28.4
	25	114.9	28.7	25	191.5	47.9
5	2-8	832.6	208.1	2-8	1857.0	464.2
	40	5.5	1.4	40	4.9	1.2
	30	13.1	3.3	30	13.2	3.3
	25	20.6	5.2	25	22.2	5.5
6	2-8	149.3	37.3	2-8	215.0	53.8
	40	10.7	2.7	40	8.8	2.2
	30	25.5	6.4	30	23.7	5.9
	25	40.1	10.0	25	39.8	10.0
7	2-8	290.5	72.6	2-8	386.5	96.6
	40	27.9	7.0	40	129.6	32.4
	30	66.4	16.6	30	349.6	87.4
	25	104.5	26.1	25	588.7	147.2
8	2-8	757.3	189.3	2-8	5709.4	1427.4
	40	23.3	5.8	40	33.6	8.4
	30	55.3	13.8	30	90.6	22.6
	25	87.2	21.8	25	152.5	38.1
	2-8	631.6	157.9	2-8	1479.2	369.8

Example 13—Forced Degradation Study of
Atropine Formulation 8 in D₂O and H₂O
Conditions

Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) was used for this experiment. A correction factor of 83.3% is used to quantitate amount of free Atropine. Table 31 shows the D₂O and H₂O formulation compositions.

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TABLE 31

Formulation 8 Compositions		
Formulation	[Free Atropine] (µg/mL)	Composition
8-D ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in D ₂ O, pD 6.2
8-H ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in H ₂ O, pH 5.8

D₂O-based Formulation 8 and H₂O-based Formulation 8 were subjected to acid, base, light, heat and oxidative stress. Approximately 5-20% degradation was targeted for all stress conditions to produce sufficient degradation while avoiding secondary degradation. At each condition, Formulation 8

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samples were incubated alongside a vehicle control containing BAK. For the light condition, a foil wrapped Formulation 8 control and foil wrapped vehicle control were prepared to understand if extraneous degradation, such as heat in the light box, were to occur. A RP-HPLC method was used to carry out the analysis. Mass balance (the correlation of potency and purity by area-%) was also evaluated using Equation I.

$$\text{Mass Balance} = \frac{(\text{Potency}_{\text{initial}} + (100 - \text{Purity}_{\text{initial}}))}{(\text{Potency}_{\text{final}} + (100 - \text{Purity}_{\text{final}}))}$$

The forced degradation results were processed at 210 nm, and are presented in Tables 32A and 32B for H₂O and D₂O formulations, respectively.

TABLE 32A

Forced Degradation Results for Formulation 8—H ₂ O								
Stress Condition		Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Control	2-8° C., foil wrapped	3 day	100.9	100.0	0.412	0.657	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	23 day	-7.9	-5.9	0.301	0.513	Y	101.8%
Base (0.001N NaOH)	Ambient, foil wrapped	4 hr	-5.2	-6.6	0.417	0.725	Y	98.7%
Heat	60° C., foil wrapped	6 hr	-7.3	-7.9	0.462	0.741	Y	99.5%
Light	Ambient, clear glass vial	7 day	-12.1	-11.9	0.428	0.478	Y	100.3%
		10 day	-18.4	-18.4	0.476	0.752	Y	100.0%
		1.1 million lux hours (10 day)	-10.1	-7.6	0.478	0.831	Y	102.5%
Light Control	Ambient, foil wrapped	1.5 million lux hours (14 day)	-19.1	-12.2	0.597	0.911	Y	107.1%
		1.1 million lux hours (10 day)	-0.4	-0.5	0.411	0.665	Y	99.9%
		1.5 million lux hours (14 day)	-3.0	-0.3	0.388	0.592	Y	102.8%
Oxidation (3% H ₂ O ₂)	Ambient, foil wrapped	3 day	-16.0	-7.9	0.532	0.791	Y	108.8%
		4 day	-28.0	-13.9	0.473	0.777	Y	115.7%
		7 day	-29.4	-13.5	0.705	0.967	Y	118.9%

TABLE 32B

Forced Degradation Results for Formulation 8—D ₂ O								
Stress Condition		Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Control	2-8° C., foil wrapped	4 day	106.7	98.3	0.361	0.659	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	17 day	-6.9	-5.5	0.250	0.469	Y	97.9%

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TABLE 32B-continued

Forced Degradation Results for Formulation 8—D ₂ O								
Stress Condition	Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance	
Base (0.001N NaOH)	Ambient, foil wrapped	5 hr	-2.3	-2.2	0.495	0.849	Y	100.0%
Base (0.005N NaOH)	Ambient, foil wrapped	30 min	-9.7	-9.6	0.601	0.894	Y	100.2%
Heat	60° C., foil wrapped	17 day	-18.1	-16.9	0.281	0.550	Y	101.1%
Light	Ambient, clear glass vial	0.44 million lux hours (4 day)	-14.1	-4.5	0.463	0.733	Y	109.6%
		0.87 million lux hours (8 day)	-24.2	-11.3	0.528	0.846	Y	113.8%
Light Control (foil covered)	Ambient, foil wrapped	0.44 million lux hours (10 day)	-0.2	1.7	0.354	0.640	Y	101.8%
		0.87 million lux hours (8 day)	0.0	1.4	0.330	0.599	Y	101.3%
Oxidation (3% H ₂ O ₂)	Ambient, foil wrapped	4 day	-10.6	-3.0	0.439	0.720	Y	107.5%
		8 day	-17.9	-8.3	0.385	0.672	Y	109.9%

Example 14—Formulation 8 Stability Comparison

The long-term stability of atropine sulfate formulation 8³⁵ in D₂O (see Table 31 for formulation composition) was analyzed at three different storage conditions. Table 33 illustrates the stability criteria: appearance, potency, tropic

acid level, total purity, and pD at storage conditions of 25° C. with 60% humidity, 40° C. with 75% humidity, and 60° C. As discussed above, $pD = PD_{reading} + 0.4$ (Glasoe, et al. “Use of glass electrodes to measure acidities in deuterium oxide” J. Physical Chem. 64(1): 188-190 (1960)).

TABLE 33

Formulation 8 Stability							
Parameter	Initial	2 weeks	4 weeks	8 weeks	6 months	9 months ²	12 months ³
Storage Condition: 25° C./60% RH							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)	99.2%	103.0%	105.0%	96.0%	99.7%	97.7%	101.7%
Tropic Acid Level	0.05%	0.11%	0.14%	0.23%	0.55%	0.91%	1.24%
Total Purity ¹	98.9%	98.9%	98.5%	98.1%	99.2%	98.4%	97.8%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.9 (pH 5.5)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.7 (pH 5.3)	5.8 (pH 5.4)
Storage Condition: 40° C./75% RH							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)	99.2%	104.8%	104.7%	94.9%	96.6%	94.2%	95.6%
Tropic Acid Level	0.05%	0.34%	0.65%	1.24%	3.32%	5.05%	6.71%
Total Purity ¹	98.9%	98.5%	97.5%	96.6%	96.3%	92.5%	90.5%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.6 (pH 5.2)	5.7 (pH 5.3)	5.5 (pH 5.1)	5.7 (pH 5.3)

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TABLE 33-continued

Formulation 8 Stability							
Parameter	Initial	2 weeks	4 weeks	8 weeks	6 months	9 months ²	12 months ³
Storage Condition: 60° C.							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay) ⁴	99.2%	101.6%	103.0%	92.9%	100.6%	104.0%	115.9%
Tropic Acid Level	0.05%	2.33%	4.02%	6.01%	10.33%	10.87%	12.97%
Total Purity ¹	98.9%	96.0%	92.8%	88.8%	85.5%	78.0%	72.4%
pD	6.3	5.6	5.5	5.2	5.1	4.9	5.0
	(pH 5.9)	(pH 5.2)	(pH 5.1)	(pH 4.8)	(pH 4.7)	(pH 4.5)	(pH 4.6)

¹Slight variability is observed in the total purity results due to sensitivity differences from one HPLC system to the next.

²Results reported are from a second aliquot taken from the original assay eyedropper.

³Results reported are from an aliquot taken from the original assay eyedropper.

⁴A growing unknown related substance peak is observed to co-elute with the main peak and is included in the Atropine Sulfate potency result due to a lack of a clear inflection point between the two species upon integration.

A comparison of Formula 8 in H₂O and D₂O under three storage conditions is further illustrated in FIG. 11. FIG. 11A shows the presence of tropic acid degradant at 25° C. with 60% humidity. By week 8, about 1.45% of tropic acid was observed in the H₂O formulation while only 0.23% of tropic acid was observed in the D₂O formulation. Similarly, at 40° C. with 75% humidity storage condition (FIG. 11B), 8.34% of tropic acid was observed in the H₂O formulation while only 1.24% of tropic acid was observed in the D₂O formulation by week 8. At 60° C. storage condition (FIG. 11C), 42.8% of tropic acid was observed in the H₂O formulation while only 6.01% of tropic acid was observed in the D₂O formulation by week 8.

Example 15—Effect of pH on Ophthalmic Acceptance in Guinea Pigs

A cohort of guinea pigs is administered 50 µl, of ophthalmic formulations having different pH values described herein. For example, ophthalmic formulations comprising H₂O or deuterated water (e.g., D₂O) are administered to the animals. Animal behavior is recorded at predetermined time intervals to evaluate the acceptance of the ophthalmic formulations

Example 16—In Vivo Rabbit Eye Irritation Test

The exemplary compositions disclosed herein are subjected to rabbit eye irritation test to evaluate their safety profile. The test composition are tested for eye irritation test in New Zealand Rabbits (see for example Abraham M H, et al., *Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis*. Toxicol Sci. 2003 December; 76(2):384-91. Epub 2003 Sep. 26; see also Gettings S D et al., *A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations*. Food Chem Toxicol. 1998 March; 36(3):209-31). The study involves single ocular administration into the right eye and the same volume of its placebo in the left eye of each of the three rabbits. Rabbits are examined immediately and after instillation of the compositions for 4, 24, 48 and 72 hours post instillation to note the signs/symptoms of eye irritation, if any. The test compositions show no sign of irritancy in cornea, iris and conjunctivae of the rabbit eyes.

Example 17—In Vivo Testing of Ophthalmic Aqueous Formulation in Guinea Pigs

Focus deprivation myopia (FDM) is achieved using a latex shield to cover one eye. For defocus-induced myopia,

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a latex-made facemask was held in place by a rubber-band around the head of animals, leaving both eyes, the nose, mouth and ears freely exposed. A—4.00 D lens is glued onto a plastic lens frame. The lens frame is then attached to the facemask around one eye by a fabric hook-and-loop fastener after the optical center of the lens was aligned with the pupil center. The lens is detached and cleaned on both sides with a water-wetted gauze at least once daily followed by re-attachment to the facemask. All the animals are maintained on a cycle of 12-h illumination (500 Lux) and 12-h darkness during the experimental period

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A cohort of guinea pigs at age of 3 weeks are randomly assigned to FDM (a facemask worn monocularly) or defocus-induced myopia (a -4.00 D lens worn monocularly) and control groups. The FDM groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or FDM-only. The defocus-induced myopia groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or defocus-only. The control groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or no treatment. Ocular biometric parameters are measured in both eyes of individual animals before and at 11 days of treatment

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Biometric parameters (e.g. refraction, corneal curvature, and axial components of the eye) are measured by an optometrist, orthoptist, or ophthalmologist with help from an animal care assistant during the light cycle (daytime) after removal of the facemask or lens. The optometrist, orthoptist, or ophthalmologist is masked in regard to the treatment conditions for each animal.

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Refraction is measured by retinoscopy after the pupil is completely dilated by topical administration of 1% cyclopentolate hydrochloride. The results of retinoscopy are recorded as the mean value of the horizontal and vertical meridians.

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Corneal curvature is measured with a keratometer modified by attachment of an +8 D lens onto the anterior surface of the keratometer. A group of stainless steel balls with diameters from 5.5 to 11.0 mm are measured by the modified keratometer. Three readings are recorded for each measurement to provide a mean result. The radius of corneal curvature is then deduced from the readings on the balls with known radii.

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A-scan ultrasonograph is used to measure axial components of the eye (lens thickness and vitreous length and axial length). The conducting velocity was 1,723.3 m/s for mea-

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surement of the lens thickness and 1,540 m/s for measurement of the vitreous length as described previously. Each of the axial components is calculated as the mean of 10 repeated measurements.

Example 18—Safety and Efficacy Studies of Ophthalmic Aqueous Formulation

A clinical trial is performed to investigate the efficacy and safety of ophthalmic aqueous formulations described herein in patents with myopia. In some instances, the study is open-label, single blind, or double blind study. Patient selection criteria include myopic refraction of at least 1.0D in both eyes, and additional factors such as astigmatism, a documented myopic progression, age, sex, and/or health conditions.

The patients are randomized to receive 0.05%, 0.01%, or 0.001 atropine aqueous formulation formulated in either H₂O or deuterated water (e.g., D₂O) once nightly in both eyes. Allocation ratio in some instances is defined based the patient population.

The patients are evaluated on day 0 (baseline), day 14, day 30, and then at 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, and 36 months. At each visit, best-corrected distance log Mar visual acuity (BCVA) is assessed by an optometrist, orthoptist, or ophthalmologist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity is assessed using best-corrected distance spectacle correction with a reduced log Mar reading chart placed at 40 cm under well-lit conditions. The near point of accommodation (NPA) is measured using a RAF rule using best-corrected distance spectacle correction. Patients are instructed to move the target inwards till the N5 print becomes slightly blurred and then outwards till it just becomes clear. Accommodation amplitude is calculated as the inverse of NPA. Mesopic pupil size is measured with Procyon 3000 pupillometer. Photopic pupil size is measured using the Neuroptics pupillometer.

Cycloplegic autorefraction is determined 30 minutes after 3 drops of cyclopentolate 1% are administered at 5 minutes apart using a Canon RK-F1 autorefractor. A Zeiss IOL Master, a non-contact partial coherence interferometry, is used to measure the ocular axial length.

The primary outcome is myopia progression over the time period of the study. Safety is assessed by adverse events including allergic reactions, irritation, or development of blurring of vision in one or both eyes.

Example 19—Preparation of an Ointment Formulation Containing Atropine Sulfate

Atropine sulfate is mixed with the dispersing agent (e.g. polyethyleneglycol) under heating and sonication and this mixture is further thoroughly mixed with a molten ointment base (e.g. a mixture of wool wax, white petrolatum, and liquid paraffin). The mixture is placed in a pressure vessel, and sterilized at 125° C. for 30-45 minutes and cooled to room temperature. In another embodiment, autoclaving is conducted under nitrogen. The resulting ophthalmic ointment is aseptically filled into pre-sterilized containers (e.g. tubes).

Example 20—Atropine-Mucus Penetrating Particle Composition

A 0.01% atropine-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-en-

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abling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200 nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15° C. and about 25° C.

Example 21—Atropine Sulfate-Mucus Penetrating Particle Composition

A 0.01% atropine sulfate-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200 nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also be added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15° C. and about 25° C.

According to another aspect of the disclosure, described herein is an ophthalmic composition that comprises from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate.

In some instances, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

In some instances, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

In some instances, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

In some instances, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

In some instances, the storage condition has a storage temperature of one of: about 25° C., about 40° C., or about 60° C. In some cases, the storage condition has a storage temperature of from about 2° C. to about 10° C. or from about 16° C. to about 26° C. In some cases, the storage condition has a relative humidity of about 60% or about 75%.

In some instances, the ophthalmic composition is in the form of an aqueous solution. In some cases, the muscarinic

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antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.04 wt %, from about 0.001 wt % to about 0.03 wt %, from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.

In some instances, the ophthalmic composition further comprises an osmolarity adjusting agent. In some cases, the osmolarity adjusting agent is sodium chloride.

In some instances, the ophthalmic composition further comprises a preservative. In some cases, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

In some instances, the ophthalmic composition further comprises a buffer agent. In some cases, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

In some instances, the ophthalmic composition further comprises a tonicity adjusting agent. In some cases, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

In some instances, the ophthalmic composition is stored in a plastic container. In some cases, the material of the plastic container comprises low-density polyethylene (LDPE).

In some instances, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some cases, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

In some instances, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

In some instances, the ophthalmic composition further comprises a pH adjusting agent. In some cases, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

In some instances, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% D₂O. In some cases, the ophthalmic composition is essentially free of D₂O.

In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

In some instances, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some cases, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

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In some instances, the ophthalmic composition is not formulated as an injectable formulation.

While preferred embodiments of the present disclosure have been shown and described herein, such embodiments are provided by way of example only. Various alternatives to the embodiments described herein are optionally employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A method of treating progression of myopia or reducing the progression rate of myopia in an individual in need thereof, comprising administering to an eye of the individual (a) an aqueous solution comprising atropine or atropine sulfate and less than about 10% of a degradant of atropine or atropine sulfate formed from degradation of the atropine or atropine sulfate and (b) a buffering agent.

2. The method of claim 1, wherein the atropine or atropine sulfate is present in the aqueous solution at a concentration of from about 0.01 mg/g to about 0.5 mg/g, from about 0.01 mg/g to about 0.3 mg/g, or from about 0.1 mg/g to about 0.2 mg/g.

3. The method of claim 1, wherein the atropine or atropine sulfate is present in the aqueous solution at a concentration of about 0.1 mg/g, about 0.2 mg/g, about 0.25 mg/g, about 0.3 mg/g, about 0.4 mg/g, or about 0.5 mg/g.

4. The method of claim 1, wherein the buffering agent comprises a borate, a borate-polyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof.

5. The method of claim 1, wherein the buffering agent comprises sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof.

6. The method of claim 1, wherein the aqueous solution further comprises a tonicity adjusting agent.

7. The method of claim 6, wherein the tonicity adjusting agent comprises a halide salt of a monovalent cation.

8. The method of claim 1, wherein the aqueous solution further comprises a viscosity agent.

9. The method of claim 8, wherein the viscosity agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, or hydroxypropylmethyl-cellulose (HPMC).

10. The method of claim 1, wherein the aqueous solution is substantially free of a preservative.

11. The method of claim 1, wherein the aqueous solution further comprises a preservative.

12. The method of claim 11, wherein a concentration of the preservative is from about 0.0001% to about 1%.

13. The method of claim 11, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

14. The method of claim 1, wherein the aqueous solution is essentially free of procaine and benacetyline, or pharmaceutically acceptable salts thereof.

15. The method of claim 1, wherein the aqueous solution is sterile.

16. The method of claim 1, wherein the aqueous solution has a pH of from about 3.8 to about 6.4.

17. The method of claim 1, wherein the aqueous solution is an ophthalmic composition.

18. The method of claim 1, wherein the aqueous solution is administered at least once a day.

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19. The method of claim 1, wherein the aqueous solution is administered once a day.

20. The method of claim 1, wherein the aqueous solution has a pH of less than 5.

21. The method of claim 1, wherein the aqueous solution further comprises a stabilizing agent.

22. The method of claim 21, wherein the stabilizing agent is selected from the group consisting of glycerol, methionine, monothioglycerol, Ethylenediaminetetraacetic acid (EDTA), ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate, magnesium, zinc and combinations thereof.

23. The method of claim 22, wherein the stabilizing agent is EDTA.

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**CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION, TYPEFACE
REQUIREMENTS, AND TYPE STYLE REQUIREMENTS**

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(b)(1) because it contains 9992 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in 14-point Times New Roman, a proportionally spaced typeface, using Microsoft Word.

Dated: February 1, 2024

/s/ Michael T. Rosato
Michael T. Rosato

*Counsel for Appellant Sydnexis,
Inc.*